NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Eltrombopag for adult patients with chronic immune thrombocytopenic purpura (cITP)

August 2012

Contents

Tables

Figures

Instructions for manufacturers and sponsors

This is the specification for submission of evidence to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. It shows manufacturers and sponsors what information NICE requires and the format in which it should be presented. NICE acknowledges that for medical devices manufacturers particular sections might not be as relevant as they are for pharmaceuticals manufacturers. When possible the specification will refer to requirements for medical devices, but if it hasn't done so, manufacturers or sponsors of medical devices should respond to the best of their ability in the context of the question being addressed.

Use of the specification and completion of appendices 1 to 13 (sections 9.1 to 9.13) are mandatory (when applicable), and the format should be followed whenever possible. Reasons for not following this format must be clearly stated. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response. The specification should be completed with reference to the NICE document 'Guide to the methods of technology appraisal' (www.nice.org.uk), particularly with regard to the 'reference case'. Users should see NICE's 'Guide to the single technology appraisal (STA) process' (www.nice.org.uk) for further details on some of the procedural topics referred to only briefly here.

If a submission is based on preliminary regulatory recommendations, the manufacturer or sponsor must advise NICE immediately of any variation between the preliminary and final approval.

A submission should be as brief and informative as possible. It is expected that the main body of the submission will not usually exceed **100 pages excluding the pages covered by the template**. The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the submission. Appendices are not normally presented to the Appraisal Committee. Any additional appendices should be clearly referenced in the body of the submission and should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the clinical-effectiveness section with 'see appendix X'. Clinical trial reports and protocols should not be submitted, but must be made available on request.

Trials should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, 'Trial 123/Jones et al.[126]' rather than 'One trial[126]').

For information on submitting cost-effectiveness analysis models, disclosure of information and equality and diversity, users should see 'Related procedures for evidence submission', appendix 10.

If a patient access scheme is to be included in the submission, please refer to the patient access scheme submission template available on request. Please submit both documents and ensure consistency between them.

Executive summary

ITP BACKGROUND

Primary immune thrombocytopenia (ITP) is an orphan disease with a prevalence of 0.05% in the UK.[1] ITP is a disorder of uncertain aetiology involving increased platelet destruction and impaired platelet production, leading to low platelet counts and impaired blood clotting. The resulting bleeding symptoms range from mild bruising to serious haemorrhage, which can be fatal.

Patients whose disease has lasted for more than 12 months are considered to have chronic ITP (cITP). They are often unresponsive to one or more agents and their disease is associated with significant morbidity, an impaired quality of life and increased mortality.

The aims of treatment are to reduce the risk of bleeding by elevating platelet count, whilst minimising treatment related side effects. The management of ITP is complex. Following first line treatment with corticosteroids or immunoglobulins there is no clearly defined treatment pathway and the RCT evidence is scarce. It is generally accepted that management of ITP is tailored to the individual patient depending on their symptoms, platelet count, lifestyle and the adverse events associated with the different therapies. Splenectomy is a potentially curative treatment option for cITP but is invasive, irreversible and not appropriate for all patients. Patients typically cycle through several therapy options, some of which have significant side effects and most of which are not licensed as treatments for ITP.

Eltrombopag is one of two thrombopoeitin receptor agonists (TPO-RAs) licensed for the treatment of cITP. In contrast to other medicines used to treat this condition, the use of both these medicines in cITP is supported by robust RCT evidence.

Rescue treatments such as intravenous corticosteroids or immunoglobulin (IVIg) may be given when a patient bleeds or is considered at high risk of bleeding. These are used either as an adjunct to the patient's primary therapy or once non-rescue treatment options have been exhausted.

ELTROMBOPAG

Eltrombopag is an oral TPO-RA that interacts with the transmembrane domain of the thrombopoietin receptor. Eltrombopag has been shown to stimulate the proliferation and differentiation of megakarocytes in the bone marrow, resulting in a dose-dependent increase in normal-functioning platelet levels. Eltrombopag is indicated in the EU for adult splenectomised c ITP patients who are refractory to other treatments and may also be considered as second-line treatment for adult non-splenectomised cITP patients where splenectomy is contraindicated.

COMPARATIVE EFFICACY

Eltrombopag raises platelet levels and reduces the risk of bleeding for patients with cITP. The RAISE trial demonstrated clinically meaningful and statistically significant differences between eltrombopag and placebo as an addition to local standard of

care, with respect to the primary endpoint, the odds of achieving a platelet count between 50 and 400x10^9/L, and pre-specified bleeding endpoints. Furthermore, it allowed patients to reduce concomitant and rescue medications. The RAISE trial stands out as providing robust evidence of clinical benefit for patients with cITP, against a backdrop of weak evidence and unlicensed therapies.

An ongoing long term extension study (EXTEND), where some patients have now been followed for over 5 years, has confirmed that eltrombopag offers long term efficacy in cITP and is generally well tolerated.

Non TPO-RA comparators relevant to the decision problem are rituximab, immunosuppressants, danazol, dapsone, cytotoxics, immunoglobulins and corticosteroids. Weighted averages for response, time to response and duration of response have been estimated for each of these; the nature of the available evidence means that it is not possible to perform direct or adjusted indirect comparisons of these treatments versus eltrombopag. In naive comparisons, eltrombopag appears to have a higher response rate, a faster time to response and a longer duration of response (with continued treatment) than other non-rescue treatments.

Romiplostim is a TPO-RA with an identical licence to eltrombopag's. Romiplostim was recommended by NICE for the treatment of cITP in 2011 (TA221). Romiplostim is administered as a weekly subcutaneous injection whereas eltrombopag is administered in the form of a daily oral tablet.

There is no direct evidence comparing eltrombopag with romiplostim. The pivotal studies for each medicine had similar inclusion criteria and comparable baseline populations and, although there are some important differences in trial designs, an adjusted indirect comparison of platelet response and bleeding rates was considered appropriate. This analysis found no statistically significant differences between the treatments. Confidence intervals around the point estimates were wide and the inherent uncertainty in such comparisons is compounded in this case by the small patient numbers and low event rates. On the other hand, clinical opinion is more certain; international (Provan 2010; Neunert 2011) and local treatment guidelines clearly consider eltrombopag and romiplostim to be interchangeable. Consistent with this, we assume no difference between the two medicines in terms of efficacy and safety in the base case of the economic evaluation, exploring the impact of the indirect treatment comparison in scenario analyses.

ECONOMIC EVALUATION

A Markov model, structurally representative of the treatment of cITP, estimated the cost-effectiveness of eltrombopag. A pathway incorporating eltrombopag was compared to a pathway without TPO-RAs (non TPO-RA pathway) and a pathway incorporating romiplostim. Costs and benefits were modelled over a patient's lifetime and the impact of alternative assumptions was explored through sensitivity analysis. The base case assumes equivalent efficacy and safety of the two TPO-RAs for all comparisons, consistent with available evidence and clinical opinion. Base case results are presented separately for splenectomised and non splenectomised

patients due to their differential prognosis (tables 1 and 2). The results incorporate patient access schemes for both TPO-RAs.

Table 1. Base-case results – splenectomised

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER (£/QALY) versus non TPO-RA pathway
Eltrombopag	£556,089	15.56	12.22	£0	0.00	Referent	Dominates
Non TPO-RA pathway	£581,073	14.35	10.95	£24,984	-1.28	Dominated	Referent
Romiplostim	£643,598	15.56	12.22	£87,508	0.00	Dominated	£48,914

Table 2. Base-case results – non-splenectomised

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER (£/QALY) versus non TPO-RA pathway
Non TPO-RA pathway	£297,292	12.78	9.55	£0	0.00	Referent	Referent
Eltrombopag	£332,193	15.03	11.86	£34,900	2.31	£15,105	£15,105
Romiplostim	£372,744	15.03	11.86	£40,552	0.00	Dominated	£32,657

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Slight discrepancies are due to rounding

Eltrombopag is cost-effective versus a non TPO-RA pathway in both splenectomised and non splenectomised patients at a threshold of £20,000/QALY in the base case. Although romiplostim is not cost-effective versus a non TPO-RA pathway in the base case analysis, a scenario analysis demonstrates that romiplostim could be considered cost-effective in this model, under a plausible set of assumptions.

Uncertainty in these cost-effectiveness estimates is acknowledged and exists as a result of variability in the treatment of ITP, the small patient numbers in an orphan disease, the heterogeneous nature of the disease and a lack of robust evidence for some comparator treatments.

Sensitivity analyses suggest that a key driver of cost-effectiveness of the TPO-RAs versus a non TPO-RA pathway is the assumed rate at which patients with platelets <50 x10^9/L receive rescue treatments. This is confirmed by an alternative evaluation which incorporated data from the eltrombopag clinical trial program and an updated systematic review. A recent study (including UK patients) of resource use in cITP demonstrated that the use of IVIg alone contributed to at least 43% of total management costs and as much as 70% in some patient groups. This suggests that the rates of rescue used in the base case are likely to be realistic estimates of rescue for at least some patients.

Assuming no difference in efficacy between the TPO-RAs, eltrombopag is significantly less costly over a lifetime (~£88,000 and £41,000/patient in

splenectomised and non splenectomised patients respectively) and is therefore cost-effective versus romiplostim in both splenectomised and non splenectomised patients. These estimates do not take into account any utility benefit which may arise from the relative convenience of oral treatment versus weekly injections.

A sensitivity analysis that incorporated the platelet response results from the indirect treatment comparison of eltrombopag versus romiplostim did not change the conclusions of the base case. Incremental analysis demonstrated that whilst eltrombopag accrued marginally fewer QALYs than romiplostim in this analysis (~0.5), it remained significantly cheaper and the preferred treatment option at a threshold of £20,000/QALY.

CONCLUSION

Eltrombopag is a clinically effective treatment for patients with cITP. The evidence for eltrombopag sits alongside a similarly robust evidence base for romiplostim, a TPO-RA with an identical therapeutic licence currently recommended by NICE for cITP patients. Not unexpectedly for an orphan condition, the comparative evidence base is uncertain, yet there is no evidence of a difference in efficacy between romiplostim and eltrombopag. The magnitude of a trial required to demonstrate non-inferiority is not feasible in an orphan disease, and even if it were possible, data would not be available within a meaningful timeframe, therefore the certainty around comparative efficacy estimates of TPO-RAs is unlikely to improve. This uncertainty should be considered alongside the substantial cost savings (acquisition and administration) available to the NHS (estimated to be ~£13,000 per patient/year for splenectomised and ~£5,000 per patient/year for non-splenectomised patients) by providing a cheaper oral alternative within the TPO-RA class.

GSK is seeking a recommendation for eltrombopag as an alternative to romiplostim which is consistent with the medicines' licences and local and international clinical guidelines. Eltrombopag provides patients and clinicians with the choice of a cheaper, oral alternative in a class of effective drugs that increase platelet counts and reduce the risk of bleeding.

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report (EPAR)), and a (draft) technical manual for devices should be provided (see section 9.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Generic name: Eltrombopag

Brand name: Revolade® (Note: eltrombopag is known as Promacta® in the US and some other non-European markets)

Approved name: Revolade 25mg and 50mg film-coated tablets

Therapeutic class: Thrombopoietin receptor agonist. ATC Code: B02BX 05

1.2 What is the principal mechanism of action of the technology?

Thrombopoietin receptor agonists (TPO-RAs) increase platelet production through activation of the thrombopoietin receptor. Thrombopoietin (TPO) is the main cytokine involved in regulation of megakaryopoiesis and platelet production. Eltrombopag is a small molecule drug that interacts with the transmembrane domain of the human TPO receptor and initiates signaling cascades similar, but not identical, to those initiated by endogenous thrombopoietin. This induces proliferation and differentiation of megakaryocytes from progenitor cells in the bone marrow, resulting in increased production of platelets.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Yes. Eltrombopag received pan-European marketing authorisation from the European Commission on 11 March 2010.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

The following information is taken from the CHMP (Committee for Medicinal Products for Human Use) assessment report for Revolade.[2]

Risk-benefit assessment

The CHMP decided that the benefits of eltrombopag outweigh the risks in splenectomised patients refractory or intolerant to first line therapies (e.g. corticosteroids and immunoglobulins). However, it judged that 'considering the unknown risks, the benefit-risk balance cannot be considered positive for non-splenectomised patients, for whom splenectomy is a therapeutic option that could potentially affect the course of the disease'. Therefore, the indication for non-splenectomised patients was restricted so that 'eltrombopag may be considered as second line treatment only when surgery is contra-indicated'.

Risk minimisation and management

The following safety concerns were identified by the CHMP at the time of the European Public Assessment Report (EPAR), and required pharmacovigilance and risk minimization activities, which are ongoing:

- Hepatotoxicity
- Post therapy recurrence of thrombocytopenia
- Haematological malignancies
- Renal tubular toxicity
- Potential for haematological changes
- Pediatric population
- Thromboembolic events
- Potential for increase in bone marrow reticulin formation
- Cataracts
- Phototoxicity
- Potential for endosteal hyperostosis
- Pregnant or lactating females

Please refer to section 2.5 of the CHMP assessment report for Revolade,[2] for a table summary of the risk management plan.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Eltrombopag is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). The indication also states that it may be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated[3].

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

Additional clinical evidence will be available in the 12 months following the submission (poster exhibition expected for December 2012), and it will be provided by interim analyses of the studies 'EXTEND (Eltrombopag eXTENded Dosing Study): An extension study of eltrombopag olamine (SB-497115-GR) in adults, with idiopathic thrombocytopenic purpura (ITP), previously enrolled in an eltrombopag study' and 'A Longitudinal 2-year Bone Marrow Study of Eltrombopag Olamine (SB-497115-GR) in Previously Treated Adults, With Chronic Immune (Idiopathic) Thrombocytopenic Purpura (ITP)'.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Eltrombopag was launched in the UK on 1 April 2010.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Eltrombopag has marketing approval in 88 countries worldwide, including European Union, European Economic Area, European Free Trade Association member states and the United States.

Eltrombopag (under the brand name Revolade®) received pan European marketing authorization on 11th March 2010 (details of the indications in section 1.5).

Eltrombopag (under the brand name Promacta®) received FDA approval in the US on 20th November 2008 for 'the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.[4]

The US label states that eltrombopag/Promacta should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. Eltrombopag/Promacta should not be used in an attempt to normalise platelet counts.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Following a full submission to the Scottish Medicines Consortium (SMC), eltrombopag was accepted by the SMC on 9 August 2010 for restricted use within NHS Scotland[5]:

SMC advice

Indication under review: Eltrombopag is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Eltrombopag

may be considered as second-line treatment for adult non splenectomised patients where surgery is contraindicated.

SMC restriction: in both the splenectomised and non-splenectomised patient populations, restricted to use in patients with severe symptomatic ITP or a high risk of bleeding.

Eltrombopag has been shown to be significantly more effective than placebo in raising and maintaining platelet counts at (or above) a minimum target level in previously treated patients with ITP.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table A1 Unit costs of technology being appraised

Pharmaceutical formulation	25 mg and 50 mg film-coated tablet, 28-tablet packs in aluminium blister
Acquisition cost (excluding VAT)	25mg x 28 tablets = £770 50mg x 28 tablets = £1,540 25 mg dose cost = £ 27.5 50 mg dose cost = £ 55 75 mg dose cost = £ 82.5 (BNF 62, List Price)
Method of administration	Oral
Doses	Dose should be individualised depending on patient's platelet count. Recommended starting dose = 50 mg once daily (25 mg for patients of East Asian ancestry). Adjust the dose to achieve and maintain a platelet count $\geq 50x10^9$/L as necessary to reduce the risk for bleeding. Use the lowest dose that is effective. Do not exceed a dose of 75 mg daily.
Dosing frequency	Once daily
Average length of a course of treatment	Eltrombopag is a continuous treatment administered daily until it is no longer effective, not tolerated or platelet levels exceed 250 x 10^9/L.
Average cost of a course of treatment	The mean dose of eltrombopag in EXTEND is 51.3mg/day. This equates to a daily cost of £56.43/day.
Anticipated average interval between courses of treatments	N/A
Anticipated number of repeat courses of treatments	N/A
Dose adjustments	See Table A2 below

Table A2 Dose adjustment of eltrombopag (Source: Eltrombopag Summary of Product Characteristics, 09/05/11)[3]

Platelet count	Dose adjustment or response
< $50x10^9$/L following at least 2 weeks of therapy	Increase daily dose by 25mg to a maximum of 75mg/day.
≥ $50x10^9$/L to ≤$150x10^9$/L	Use lowest dose of eltrombopag and/or concomitant ITP treatment to maintain platelet counts that avoid or reduce bleeding.
>$150x10^9$/L to ≤ $250x10^9$/L	Decrease the daily dose by 25mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> $250x10^9$/L	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤ $100x10^9$/L, reinitiate therapy at a daily dose reduced by 25mg.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

Prior to initiation of eltrombopag, a peripheral blood smear should be examined closely to establish a baseline level of cellular morphologic abnormalities. Eltrombopag may increase the risk for development or progression of reticulin fibres within the bone marrow. The relevance of this finding, as with other thrombopoietin receptor (TPO-RA) agonists, has not been established yet [3].

Eltrombopag is an oral medication and can be self administered by patients at home.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

The monitoring requirements are as follows[3]:

- Serum ALT, AST and bilirubin should be measured prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. Abnormal serum liver tests should be evaluated with repeat testing within 3 to 5 days. If the abnormalities are confirmed, serum liver tests should be monitored until the abnormalities resolve, stabilise, or return to baseline levels.
- Routine monitoring of patients for cataracts is recommended.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Eltrombopag can be taken in addition to other ITP medications if required. The dose regimen of concomitant ITP treatments should be modified as medically appropriate, to avoid increases in platelet counts to more than $150x10^9/L$ during therapy with eltrombopag.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Definitions

Immune thrombocytopenic purpura (ITP; formerly known as idiopathic thrombocytopenic purpura, and also known as immune thrombocytopenia) is a rare disorder recognised as an orphan disease by the EMA (defined as a life threatening or chronically debilitating condition affecting fewer than 5 per 10,000 persons). It is characterised by a combination of autoimmune destruction of platelets and impaired platelet production. This results in low platelet count (thrombocytopenia), which impairs blood clotting. ITP occurs in both children and adults. ITP in adults generally follows a chronic course [6-8]. This submission refers only to adult chronic ITP (cITP).

Standard definitions were published by an International Working Group (IWG) consisting of recognised expert clinicians in 2009[9].

- Primary ITP is defined as isolated thrombocytopenia (in the absence of anemia and neutropenia), with a platelet count less than $100x10^9$/L, without other causes. It is a diagnosis of exclusion, with no robust diagnostic markers apart from platelet count. In the past, a threshold of $150x10^9$/L was used[9].
- Varying definitions of cITP have been used. In an effort to standardise, chronic disease in adults was redefined by the International Working Group in 2009 as at least 12 months' duration from a previous definition of 6 months, with duration of 3-12 months given a new designation of 'persistent disease'[9], and 0 to 3 months defined as 'newly diagnosed'. However, these definitions have not been formally validated[10].
- Disease severity was previously correlated with the degree of thrombocytopenia disregarding the presence or absence of bleeding symptoms. However, the IWG agreed that the term "severe" ITP should be used only in patients who have clinically relevant bleeding (defined by the presence of bleeding symptoms at presentation sufficient to mandate treatment, or by the occurrence of new bleeding symptoms requiring additional therapeutic intervention with a different platelet-enhancing agent or an increased dose)[9].

The goal of treatment is to prevent major bleeding episodes by raising platelet count to a 'safe' level, while minimising treatment-related side effects[9]. The minimum safe platelet count is generally considered to be $>30x10^9$/L. Treatment does not aim to restore platelet counts to normal levels.

Epidemiology

Incidence

By its nature, incidence data refers to newly diagnosed cases. Although some patients do experience permanent remission, ITP in adults generally follows a chronic course[6-8]. Thus, the majority of incident cases will go on to become chronic. A 2010 systematic review and critical analysis on ITP epidemiology[11] found only three original published studies on ITP incidence in adults, with values ranging from 1.6 to 3.9/100,000/year. Two of these were from the UK.

The most robust estimate of ITP incidence (based on methodology) was judged by Terrell et al.[11] to come from Denmark[12]. For adults with platelet counts $<100x10^9$/L presenting after 1985, the annual incidence estimate was 3.3/100,000.

Prevalence

A study of ITP prevalence in the UK was conducted by GlaxoSmithKline using the General Practice Research Database (GPRD)[1].

- The age- and gender-adjusted, overall 18-year period prevalence was 0.05% (50/100,000, 95% CI [49.20-50.90] persons).
- There were 24,337 (95% CI [23,948-24,775]) prevalent adult cases of diagnosed ITP in the UK in 2009.
- Prevalence rose with age, from 30/100,000 at age 18-49 to 93/100,000 at age ≥65 years.
- Prevalence was higher among females (59/100,000) than males (40/100,000).

A large US study by the same authors (Feudjo-Tepie 2008) found an age-adjusted prevalence of diagnosed cITP of 23/100,00[1;13].

Pathophysiology and disease course

Platelets are formed by the maturation of precursor cells known as megakaryocytes in the bone marrow, under the control of thrombopoietin and a complex network of cytokines, chemokines and growth factors. ITP is an autoimmune disease in which autoantibodies bind to platelets, leading to platelet destruction by macrophages in the spleen and/or liver[14]. The autoantibodies in ITP also enter the bone marrow and bind to megakaryocytes, reducing platelet production and contributing further to low platelet counts[14;15]. The cause of autoantibody development is unknown.

Clinical presentation

In adults, ITP typically has an insidious onset, with no preceding viral or other illness, and a chronic course[6;8].

The clinical manifestations of cITP are highly variable[7;10]. It is fairly common for patients to be asymptomatic or develop only mild bruising or petechiae[6]. Others may have episodes of spontaneous bruising or serious muco-cutaneous bleeding. The most serious complication of ITP is intracranial haemorrhage or bleeding at other internal sites (e.g. gastrointestinal tract). This is rare, but can be fatal[16;17].

Platelet counts[7], are often used as a surrogate for the risk of bleeding, but bleeding at particular counts is not inevitable. Age, lifestyle factors and presence of uraemia also contribute to bleeding risk[7].

- Bleeding symptoms are infrequent in patients with platelet counts over $50x10^9$/L. Risk and severity of bleeding increase as platelet count drops below this level[16;18].
- Symptoms such as severe cutaneous bleeding, prolonged epistaxis, gingival bleeding or menorrhagia may be more frequently observed at platelet counts of $10x10^9$/L to $20x10^9$/L[16;19].
- Patients with a platelet count of less than $10x10^9$/L (and usually below $5x10^9$/L) are at greatest risk for serious internal bleeding, including intracranial haemorrhage[16;20;21].
- Risk of serious or fatal bleeding increases with age[9].

Mortality and morbidity

Most fatal bleeding has been reported to occur in patients with platelet counts $<30x10^9$/L[9].

Cohen *et al.* estimated the annual rate of fatal bleeding events in ITP patients with persistently low platelet counts ($<30x10^9$/L) at between 1.62% and 3.89%. Predicted 5-year mortality rates from bleeding events ranged from 2.2% for patients under 40 years to 47.8% for those older than 60 years[22].

Danese *et al.* estimated that there were 129,000 hospitalisations for ITP in the US between 2003 and 2006[17]. The overall in-hospital mortality rate for ITP patients was 3.8%.

A cohort study in the Netherlands found that the all cause mortality risk of ITP patients within 2 years of diagnosis was 1.3 (95% CI [0.89-2.0]) times that of the general population. Patients with platelet counts persistently below $30x10^9$/L had a 4.2 (95% CI [1.7-10.0]) fold risk[21].

Morbidities associated with severe cITP are non-fatal bleeding episodes sometimes requiring hospitalisation (especially gastrointestinal and intracranial haemorrhage); increased risk of infection; rash (purpura or petechiae; caused by bleeding under the skin); severe mucosal haemorrhage; bleeding after surgery or trauma.

In a retrospective analysis of 310 patients with cITP, 8% of patients had major bleeding (defined as requiring hospital admission or with a clinically overt fall in haemoglobin of ≥2g/dL) and 44% had minor bleeding (purpura, ecchymoses, gum bleeding or mild epistaxis) at diagnosis[23].

Quality of life

Several studies have clearly demonstrated diminished health-related quality of life (HRQoL) in patients with ITP[24-26]. HRQoL is affected by disease symptoms, fear and anxiety about platelet levels and possible bleeding episodes, and the side effects of

treatment. Over 80% of patients in focus group discussions reported that ITP interfered with the ability to work[27].

Concerns about the side effects of treatment are a well documented determinant of HRQoL in patients with ITP[27]. These often lead to dose reductions or treatment discontinuation[28]. Corticosteroid therapy is associated with the greatest number of bothersome and potentially serious side effects [28;29].

GSK approached several ITP specialists with a request to collect descriptive patient case studies for the purpose of inclusion within this NICE submission. Clinicians were asked to identify patients with chronic (>12 months) ITP who required substantial medical input / clinical care with regards to treatment, follow-up and hospitalisation. Selected patients need not be receiving a TPO receptor agonist or any other active chronic treatment; the purpose of the exercise was not to illustrate the effects of particular treatments.

The objective of the case studies was to provide a qualitative depiction of the impact of ITP on these patients' quality of life – emotional and physical, and the impact on healthcare resources. GSK provided a template to guide the collection of information.

GSK received 5 case studies from two ITP specialists. These are provided in Appendix 13 in the form of the templates provided by GSK and completed by clinicians.

The case studies depict patients with cITP and demonstrate the impact of the disease on their mental and physical health. The side effects as a result of receiving ITP treatments as well as the impact on the quality of life are also described. The impact on the ability to play sport or plan holidays due to uncontrolled symptoms is also described, as well as the anxiety associated with the uncertainty of fluctuating platelet levels. These case studies also demonstrate that patients with ITP respond to a treatment for a period of time, before relapsing and then are considered for other treatment options (consistent with the approach to treatment described in international treatment guidelines). For patients who are uncontrolled on treatment, rescue therapy, including IVIg, is often prescribed, and the case studies demonstrate that at least for some patients, IVIg is prescribed repeatedly over the course of a year.

2.2 How many patients are assumed to be eligible? How is this figure derived?

NICE has previously estimated that the number of patients with severe cITP and at high risk of bleeding, or who are refractory to standard treatment, represents around 1-4% of the total population with ITP[30].

Based on an estimated 20,118 patients with ITP in the UK (derived from the prevalence reported by Bennett et al[1], the assumptions set out in the NICE romiplostim costing template[31] have been used to estimate the number of patients who would be eligible for treatment with eltrombopag (Table A3). This results in an estimate of 485 eligible patients per year. This corresponds to approximately 2.4% of all patients with ITP, which is within the range of the NICE estimate.

Table A3 Derivation of the number of patients estimated to be eligible for eltrombopag

UK adult population (≥18 years): 40,235,268 Estimated prevalence ITP = 0.05% of population [1]		
	Proportion of pts	**Number of pts**
Patients with ITP	100%	20,118
Pts requiring treatment	60%	12,071
1st line treatment unsuccessful	67% (of those treated)	8087
Pts requiring long-term treatment	40% (of those in whom 1st line treatment failed)	3235
Pts remitting or responding to other treatments	85% (of those in long-term ttmt)	2749
Pts who may use a TPO-RA	15% (of those in long-term ttmt)	485

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

NICE has not issued clinical guidelines for ITP. Two single technology appraisals have been undertaken, both covering the use of thrombopoietin receptor agonists in their licensed indications.

Thrombocytopenic purpura – eltrombopag (TA 205, October 2010)[32]

Eltrombopag was not recommended within its marketing authorisation for the treatment of chronic immune (idiopathic) thrombocytopenic purpura.

Thrombocytopenic purpura – romiplostim (TA 221, April 2011)[33]

Romiplostim is recommended for the treatment of adults with chronic immune (idiopathic) thrombocytopenic purpura:

- whose condition is refractory to standard active treatments and rescue therapies **or**
- who have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies

and

- if the manufacturer makes romiplostim available with the rebate on the list price agreed under the patient access scheme.

Only a haematologist should start and supervise treatment with romiplostim.

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

Background

- An International Consensus Report was published in 2010[7], and the American Society of Hematology published a guideline in 2011[10]. Both these documents have been influential in the UK, particularly the international consensus report. Several NHS Trusts have published ITP treatment protocols[34-36].
- The majority of adult patients with newly diagnosed ITP will eventually become chronic, following the persistent phase of the disease.[7]
- The first line treatment for newly diagnosed ITP patients is well estabilished, and includes the use of corticosteroids (or IVIg if steroids are contraindicated); the majority of patients will however become refractory or experience intolerable long term side effects. Regardless of their current disease phase (newly diagnosed, persistent or chronic), most patients will therefore require a second line treatment, which includes a number of different therapeutic options. There have been only few randomised controlled trials from which to formulate an evidence-based approach in the choice of a specific second line treatment. As a result, the management of ITP beyond first line treatment with corticosteroids varies widely[7].
- As noted by the International Consensus Report, second line 'treatment related decisions still remain principally dependent on clinical expertise or patient preference rather than high-quality clinical trial evidence'[7].
- Treatment is considered appropriate for patients who are symptomatic, and those who are at significant risk of bleeding. As well as platelet count, factors taken into account when deciding on whether to treat may include lifestyle, comorbidities predisposing to bleeding, patient anxiety about bleeding, willingness to tolerate side effects, and any planned (e.g. surgical) interventions[7].
- Asymptomatic patients with no significant bleeding risk are not routinely treated simply to raise their platelet counts. Patients are more likely to be considered for treatment once platelet levels fall below $50x10^9/L$[7].
- Treatment options available, regardless of the disease phases, are summarised in Table A4. A generalised treatment pathway reflecting UK clinical practice is shown in Figure A2. Please note that current guidelines do not necessarily reflect the licence status of the treatments mentioned.

Table A4 Summary of treatment options in ITP by line. Sources: Provan 2010[7], Neunert 2011[10]

Treatment line	Agents	Notes
First line (Newly diagnosed)	Corticosteroids **If corticosteroids contraindicated:** IVIg (intravenous immunoglobulin) 1-2 days	Corticosteroids (prednisolone 1-2 mg/kg/day) are given for 10-28 days then tapered off regardless of response, because of risk of adverse effects.
Second line	**Medical** Any of the following agents may be used: Azathioprine Cyclosporin A Cyclophosphamide Danazol Dapsone Mycophenolate mofetil Rituximab (4 weeks) Thrombopoietin receptor agonists (TPO-RAs) Vinca alkaloids **Surgical** Splenectomy	Rituximab is usually given as a single course. The other agents may be given continuously or may be subject to a trial of discontinuation; a proportion of patients have sustained response off therapy, varying from months to years (with the exception of mycophenolate and TPO-RAs, which are not associated with sustained off-treatment response)[7]. TPO-RAs stimulate platelet production rather than modulating the immune system and must be admistered continuously Selection of therapy is individualised according to patient and physician preference and individual tolerance Splenectomy is rarely performed before 12 months from diagnosis in the UK
Third line*	Thrombopoietin receptor agonists Splenectomy	
Emergency treatment for severe bleeding	Platelet transfusion IVIg Intravenous (IV) corticosteroids	

* Third line treatments with minimal data are alemtuzumab, combination first and second line treatments and haematopoetic stem cell transplantation.

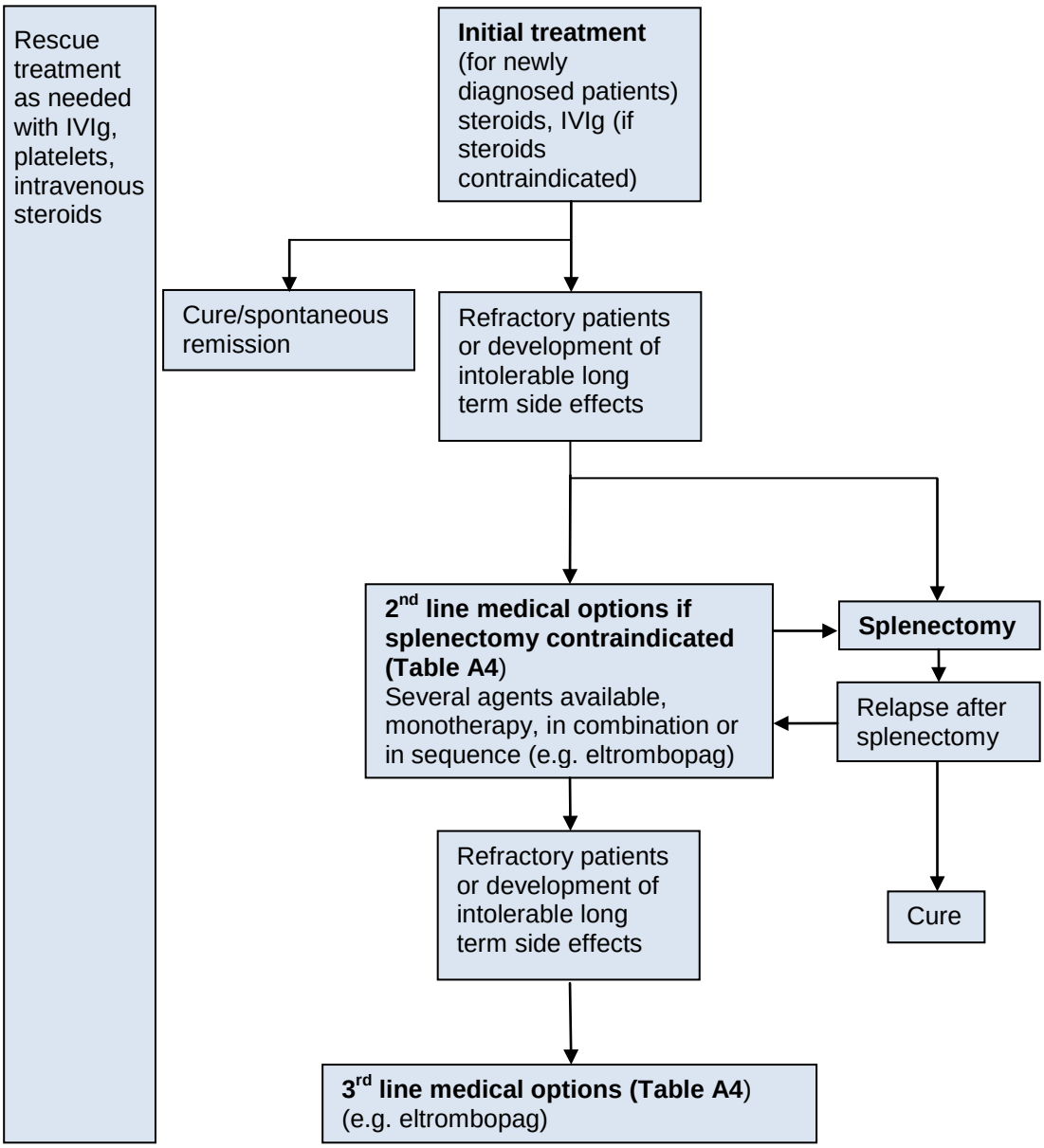


Figure A1 Generalised treatment pathway for ITP

Initial (first line) treatment of newly diagnosed ITP

A short (10-28 day) course of oral corticosteroids is the preferred first line treatment.

Corticosteroid therapy is not prolonged because of the risk of adverse effects[7;10]. Intravenous immunoglobulin (IVIg) (1-2 infusions) can be used if steroids are contraindicated[7;10]. Response to these agents is usually transient[7].

Second line medical options

As previously mentioned, regardless of the disease phase (newly diagnosed, persistent or chronic), most patients will need splenectomy if not contraindicated, or a second line agent. The International Consensus Report[7] noted that a lack of high quality clinical trials, and the lack of a consistent definition of response mean it is not possible to meaningfully compare response rates for different treatments in those studies that are available, and therefore was not possible to recommend any particular second line agents in Table A4 more strongly than others.

Selection of second line therapy is individualised according to patient and physician preference and individual tolerance. A series of second line therapies may be tried in sequence or in combination, until one is found that is effective and well tolerated for the individual patient. Most patients will require continuous treatment: for some, low-dose maintenance is sufficient. Some patients experience intermittent relapses on second line therapy that can be managed by rescue treatment, e.g. IVIg,intravenous steroids, platelet transfusion).

A minority of patients will experience sustained off-treatment response after a course of second line therapy. These patients are likely to follow a pattern of monitoring and intermittent treatment when platelet counts fall unacceptably low and/or unacceptable symptoms reappear.

Thrombopoietin receptor agonists

The International Consensus Report (Table A4) and The American Society of Hematology 2011 guidelines include TPO-RAs both as second and third line treatment options (11;15), however, the licences for TPO-RAs eltrombopag and romiplostim state that they may be considered as second line treatment for adult non-splenectomised cITP patients only where surgery is contraindicated.

The optimal positioning of the TPO-RAs in the second line treatment pathway (when splenectomy is contraindicated) in relation to rituximab and other second line agents is uncertain[10]. Local UK guidelines suggest that currently they are mainly used after rituximab[35].

A patient (n=203) and physician (n=50) market research survey was carried out by GSK to determine treatment preferences for patients with ITP. The strict dietary requirements needed with eltrombopag treatment were a limiting factor, however after being provided with simplified drug profiles for both romiplostim and eltrombopag, derived mean scores indicate that patients and physicians did not show any strong preference for one over the other. This demonstrates a demand for an oral alternative to romiplostim[37].

Second line surgical option

Splenectomy

Splenectomy is a viable second line treatment choice; however, given the existence of a small possibility of disease remission within 12 months from the diagnosis, this procedure is usually deferred until and only considered in patients with ITP in its chronic phase. Splenectomy is curative in approximately two thirds of patients who receive it[7], and therefore is the second line treatment of choice in chronic ITP in some UK centres. It must be taken into account that about 14% do not respond to splenectomy, and a further 20% relapse after initial response[7]. The patients' fitness for surgery, their compliance, the risk to develop procedural complications, and the long term immune suppression are carefully considered when considering treatment with splenectomy. Some centres now carry out platelet kinetics evaluations (indium labelled autologous platelet scanning) before splenectomy as a response prediction test, and restrict surgery to patients in whom the spleen is shown to be a major site of platelet destruction.

Those patients who do not achieve satisfactory platelet counts long-term[7] may require further medical treatment.

Third line medical options

A small group of patients experiences severe disease that is refractory to second line medical options. These patients may be considered for splenectomy; if contraindicated, patients and physicians can consider a third line medical option.

Thrombopoietin receptor agonists

The TPO-RAs are the only medical treatment listed by the international guidelines as Category A (treatment options with sufficient data) or Grade 1 recommendations in patients refractory to conventional treatments[7;10].

- The International Consensus Report 2010 recommends TPO-RAs for patients in whom first and second line therapies failed[7].
- The American Society of Hematology 2011 guidelines recommend TPO-RAs 'for patients at risk of bleeding who relapse after splenectomy or who have a contraindication to splenectomy and in whom at least one other therapy has failed' (grade 1B recommendation)[10]. They also suggest that 'thrombopoietin receptor agonists may be considered for patients at risk of bleeding in whom one line of therapy such as corticosteroids or IVIg has failed, and who have not had splenectomy' (grade 2C recommendation).
- Based on the results of phase III clinical trials, TPO-RAs have identical licensed indications, and are referred to as a class in these guidelines[7;10].

The other available third line options (alemtuzumab, combinations of first and second-line therapies, combination chemotherapies and hematopoietic stem cell transplantation) are all categorised as Category B (treatment options with minimal data) and considered to have potential for considerable toxicity[7].

The TPO-RAs thus address a previously unmet need for an effective, well tolerated therapy for the small group of severe ITP patients who do not achieve acceptable disease control using other therapies.

Rescue therapy

Patients with ITP on treatment may need additional therapeutic interventions, in terms of IVIg, intravenous corticosteroids, platelet transfusion.

IVIg treatment, given its cost and the associated risk of infections, is only used in a regular preventive setting, in cITP, for patients refractory to multiple treatments with a predictable risk of bleeding.

Anticipated role of eltrombopag

As eltrombopag is licensed for the same indication as romiplostim, and in view of the overlapping populations in the phase III trials of the two agents, it is anticipated that eltrombopag will be incorporated into the UK treatment pathway in the same manner as romiplostim. As a market research survey has indicated, there is a near equal preference for the drug profiles of eltrombopag and romiplostim[37]. The availability of eltrombopag will offer patients and physicians a choice of agent within the TPO-RA class, including the option of an orally administered therapy with simple dosing.

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

As explained in Section 2.4, clinical practice varies widely, due to the lack of good quality evidence comparing the relatively numerous treatment options. This is compounded by the heterogeneity of the disease, and the fact that treatment is individualised for each patient.

The availability of rituximab (despite not being licenced for ITP) and the TPO-RAs has opened up new questions on treatment sequencing.

However, the guideline notes that ‘there is no evidence to guide a sequence of treatments for patients who have recurrent or persistent thrombocytopenia associated with bleeding after an initial treatment course with corticosteroids (or IVIg or anti-D)’(15).

2.6 Please identify the main comparator(s) and justify their selection.

A pathway of care incorporating eltrombopag will be compared to:

- A pathway of care without the use of TPO-RAs (non-TPO-RA pathway)
- A pathway of care incorporating romiplostim

The non-TPO-RA pathway is included as it is likely that both romiplostim and non-romiplostim-containing treatment pathways are currently followed in the UK, given the heterogeneity in second and subsequent line therapy use.

Romiplostim is an appropriate comparator because it is licensed for the same patient population as eltrombopag and also because it is recommended for cITP by NICE. Romiplostim and eltrombopag are treated as interchangeable in international and local treatment guidelines, and are viewed as interchangeable by clinicians.

TPO-RAs could be positioned as either second or third line within the non-TPO-RA pathway as per guidelines and the licenced indication.

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Not applicable.

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Location of care, staff usage and administration costs

Eltrombopag treatment should be initiated by, and remain under the supervision of, a physician experienced in the treatment of haematological diseases. This often takes place in specialist centres where physicians have expertise in platelet disorders.

Eltrombopag is an oral medication that can be self-administered by patients at home. There are no staff or other costs associated with administration other than dispensing costs.

Monitoring requirements

The following monitoring requirements are specified in the eltrombopag Summary of Product Characteristics [3]:

- Prior to initiation of eltrombopag, the peripheral blood smear should be examined.
- Serum ALT, AST and bilirubin should be measured prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase.
- Routine monitoring of patients for cataracts is recommended.
- Standard monitoring of patients with ITP including full blood counts will occur irrespective of treatment.

Staff usage and costs

Other than the routine monitoring outlined above, no additional resource use is anticipated.

2.9 Does the technology require additional infrastructure to be put in place?

No.

3 Equity and equality

NICE considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and other methods, research into technology uptake in different population groups, evidence on differential treatment effects in different population groups, and epidemiological evidence on risks or incidence of the condition in different population groups.

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

No issues relating to equity or equalities were identified.

3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

No issues relating to equity or equalities were identified.

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

N/A

4 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with immune (idiopathic) thrombocytopenic purpura, who • have had a splenectomy and are refractory to other treatments (e.g. corticosteroids, immunoglobulins) • who have not had a splenectomy and for whom surgery is contraindicated, as second line treatment	Adults with chronic immune (idiopathic) thrombocytopenic purpura, who • have had a splenectomy and are refractory to other treatments (e.g. corticosteroids, immunoglobulins) • who have not had a splenectomy and for whom surgery is contraindicated, as second line treatment	
Intervention	Eltrombopag	Eltrombopag	
Comparator(s)	•Corticosteroids intravenous normal immunoglobulin •immunosuppressive agents including rituximab • romiplostim	The cost-effectiveness model will compare a pathway of care incorporating eltrombopag to: • A pathway of care without the use of TPO-RAs (non-TPO-RA pathway) • A pathway of care incorporating romiplostim The non-TPO-RA pathway of care comprises a sequence of rituximab, azathioprine, mycophenolate mofetil, ciclosporin, dapsone, danazol, cyclophosphamide, vincristine and vinblastine. The positioning of TPO-RAs within this pathway in either a second or third line setting as per the guidelines and licence will be explored. Patients may also receive rescue treatment consisting of IVIg, IV corticosteroids or platelet transfusion.	

Outcomes	The outcome measures to be considered include: • platelet count • response rate • duration of response • need for rescue treatments • use of concurrent treatments • reduction in symptoms (minor and/or severe) • mortality • adverse effects of treatment • health-related quality of life	The outcome measures considered will be: • platelet count • response rate • duration of response • time to response • need for rescue treatments • use of concurrent treatments • reduction in bleeding symptoms • mortality • adverse effects of treatment • health-related quality of life	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The time horizon for the economic evaluation will be based on the appropriate time period over which costs and benefits can reasonably be expected to be experienced given the chronic nature of the condition. The analyses should consider the comparison of treatment sequences with and without eltrombopag, and the frequency of rescue therapies. The analyses must specify if eltrombopag is an addition to, or a replacement of an existing element in, the treatment pathway. Costs will be considered from an NHS and Personal Social Services perspective.	The modelled health benefits will be expressed in terms of life years (LYs) gained and quality adjusted life years (QALYs) gained and the cost-effectiveness in terms of incremental cost per LY and cost per QALY gained. A lifetime time horizon will be used in the cost-effectiveness model. A treatment sequence including eltrombopag will be compared to treatment sequences without eltrombopag. The impact of different treatment sequences, the positioning of eltrombopag in the sequence and the frequency of rescue will be explored through sensitivity analysis. The model will take a National Health Service (NHS) perspective and 2011 will be used as the costing year.	

Subgroups to be considered	Consideration will be given to subgroups of patients who have • undergone splenectomy • not undergone splenectomy where surgery is contraindicated. If the evidence allows, other subgroups may be identified for whom the technology may be particularly clinically and cost effective.	Results will be presented separately for splenectomised and non splenectomised patients	
Special considerations, including issues related to equity or equality		No equity or equality issues have been identified for adult patients with chronic ITP.	

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY(s), quality-adjusted life year(s)		

5 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

- Eltrombopag is one of two licensed drugs in a new class of treatments for chronic ITP (cITP) – thrombopoietin receptor agonists (TPO-RAs) - which work by activating the TPO receptor thereby stimulating platelet production.
- Eltombopag has been shown through three randomised, double-blind placebo controlled trials (TRA 10773A, 10773B and 102537 (RAISE)) to be an effective, well-tolerated treatment for patients with refractory/relapsed cITP. Each of these trials, at the time of being conducted, was the largest placebo-controlled study in cITP. These three studies combined, comprise the largest placebo-controlled RCT database for any agent in the treatment of cITP.
- RAISE enrolled patients with relapsed/refractory disease, 74% of whom were experiencing bleeding symptoms at baseline. The RAISE trial demonstrated clinically meaningful and statistically significant differences between eltrombopag and placebo arms with respect to the primary endpoint, the odds of response, and with respect to pre-specified bleeding endpoints.
- Long term efficacy and tolerance has been demonstrated through an ongoing open label long term extension study (EXTEND) which has so far followed patients receiving eltrombopag for up to 4.5 years.
- No randomised, controlled trial has directly compared eltrombopag to other treatments for cITP in adults; the two eltrombopag phase III trials undertaken so far (TRA 100773B and RAISE) have evaluated the combination of eltrombopag + local standard of care versus placebo + local standard of care.
- Romiplostim was also shown, through two randomised, double-blinded placebo controlled trials to be a well-tolerated effective treatment for patients with relapsed/refractory cITP (Kuter 2008).
- An adjusted indirect comparison of platelet responses and bleeding events between eltrombopag and romiplostim showed no statistically significant differences between the two treatments. Although the patient populations included in RAISE and Kuter 2008 are similar, differences in the trial designs with respect to study endpoints, platelet measurement, collection of bleed data and the allowance of rescue medications make it difficult to directly compare endpoints across trials.
- The evidence for eltrombopag and romiplostim does not support use of one treatment in preference to the other. This is reflected by the recommendations issued by the expert panels in the recent guidelines for ITP which do not discriminate between the two.
- Evidence for non-TPO-RA treatments was poor, with few RCTs available.
- A naïve indirect comparison was carried out comparing the efficacy of eltrombopag to non-TPO-RAs. Eltrombopag was shown to have a favourable response, time to response and duration of response compared to non-TPO-RA treatments.
- Eltrombopag has been shown to be a well-tolerated and effective treatment for relapsed/refractory cITP. The convenience of oral administration makes it an important alternative to romiplostim.

5.1 Identification of studies

Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section **Error! Reference source not found.**.

A systematic review of the literature was carried out in Embase, Medline and Medline In-process using the OvidSP service provider and CENTRAL via the Cochrane Library. The original searching was carried out in May – June 2009, with an identical update performed in February 2012. The update search was run from January 2009 to ensure no studies were missed (any studies retrieved by the initial review were excluded at abstract review in the update review). Full search syntaxes for each search are provided in Appendix 2.

In addition, conference abstracts from 2004 to present from the American Society of Hematology (ASH) and the European Haematology Association (EHA) annual conferences were searched for relevance. Where available conference abstracts were searched using Embase (OvidSP). If the conference proceedings could not be searched using Embase then conference abstract booklets were searched online using free text terms for "Idiopathic thrombocytopenic purpura, Idiopathic thrombocytopaenic purpura, Thrombocytopenia, Thrombocytopaenia, ITP". Searches for the 2004-2009 conference proceedings were carried out in June 2009, with proceedings from 2009-2012 carried out in February 2012 as part of the update. The complete search syntaxes are provided in Appendix 2.

5.2 Study selection

5.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

The inclusion and exclusion criteria implemented for study selection are provided in Table B5.

Table B5 Eligibility criteria used in search strategy for clinical effectiveness studies

Clinical effectiveness	
Inclusion criteria	
Population	Adults (≥18 yr) diagnosed with primary ITP and platelet counts <30 $X10^9$/L
Interventions	Evaluated ≥ 1 of the following treatments: eltrombopag, romiplostim, dexamethasone, methylprednisolone, danazol, dapsone, IV-Ig, IV anti-D, rituximab, azathioprine, cyclosporine, mycophenolate, vincristine, vinblastine, cyclophosphamide, or autologous stem cell transplantation or any combination of the above treatments.
Outcomes	Reported ≥1 of the following outcomes Efficacy: • Platelet count (median, response rate, durability of response) • Use of rescue and/or concomitant ITP medication • Symptom reduction • Adverse Events • Bleeding events (incidence, severity and outcome) • Mortality Health related quality of life
Study design	Prospective clinical studies (RCT and non-RCT) and retrospective studies including ≥ 10 patients.
Language restrictions	English Language studies only
Exclusion criteria	
Population	Subjects with any secondary ITP
Interventions	Splenectomy (i.e. studies reporting the outcome of the splenectomy procedure)

Searches were not restricted to patients with cITP, due to poor reporting of whether patients had cITP in the published literature.

The original systematic review (June 2009) retrieved studies reporting splenectomy as a treatment. As eltrombopag is indicated for patients who have already received or are contraindicated for splenectomy, this comparator was deemed inappropriate for inclusion in this submission. Studies reporting on the splenectomy procedure were excluded from the updated review (February 2012) and were removed retrospectively from the original review.

5.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 5.2.4.

PRISMA diagrams for the initial and updated searches are provided in Figure B3 and Figure B4. Hereafter, results of the two systematic reviews will be combined. Search

syntaxes were designed to capture studies of all relevant drugs identified. Eltrombopag studies are presented in section 5.2, romiplostim studies in section 5.7 and those for non-TPO-RA agents in section 5.8.

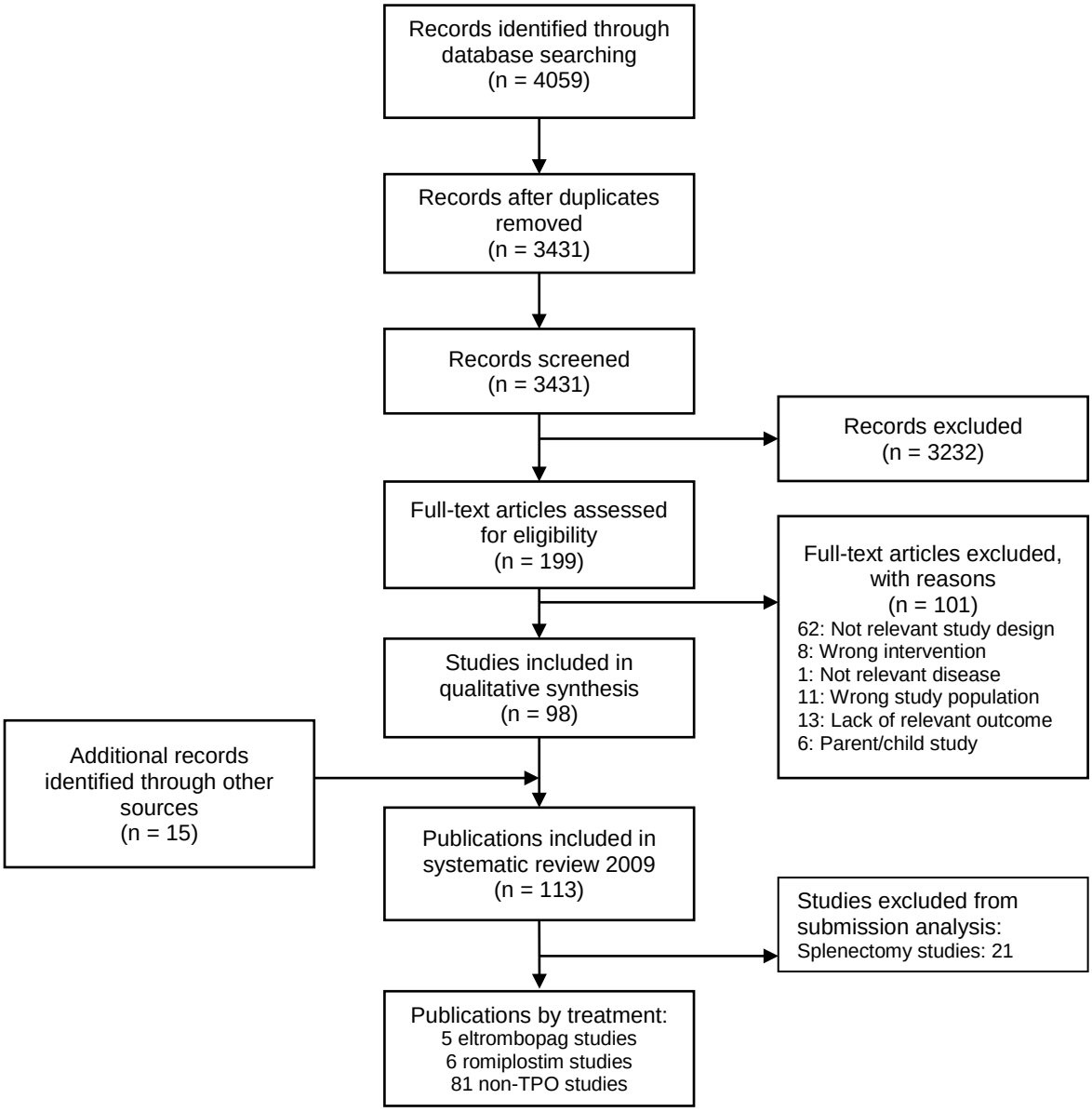


Figure B3 PRISMA diagram of included studies from the initial systematic review in June 2009 (database inception to June 2009)

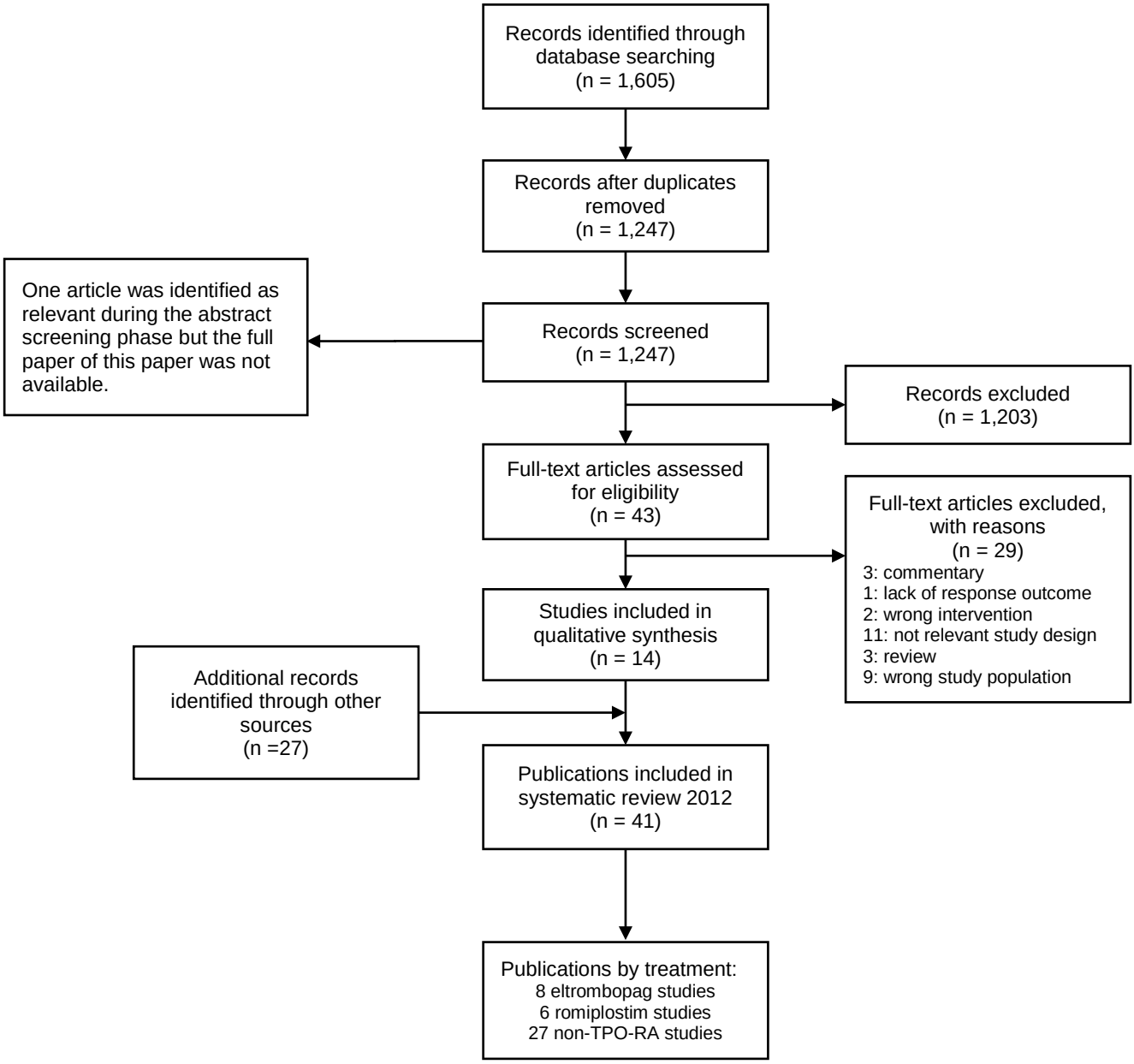


Figure B4 PRISMA diagram of included studies from the updated review in February 2012 (June 2009 to February 2012)

5.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Data for the RAISE study was drawn from the following sources; Cheng 2011 (Lancet publication) and the associated clinical study report (CSR)[38;39]. Data for the TRA 100773A study was drawn from Bussel 2007 and the associated CSR[40;41], and data from the TRA 100773B study was drawn from Bussel 2009 and the associated CSR[42;43].

TRA 105325 EXTEND[34;36;44-46] represents an open-label extension of the previous eltrombopag RCTs; TRA 100773A, TRA 100773B and RAISE, as well as a non-RCT (REPEAT[47]). A full evaluation of EXTEND is carried out in section 5.9.

Complete list of relevant RCTs

5.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

A complete list of included eltrombopag studies is provided in Table B6.

Four RCTs were identified: three full papers and one conference abstract, all comparing eltrombopag to placebo. TRA 100773A[40] is a phase II dose finding study for eltrombopag, and TRA 100773B[42] is a phase III trial assessing the safety and efficacy of eltrombopag with a 6 week treatment period. RAISE assessed the safety and efficacy of eltrombopag with a 6 month treatment period[38;39].

Table B6 List of relevant RCTs

Trial no.	Intervention	Comparator	Population	Primary study ref.
TRA 100773A[40]	Eltrombopag 30 mg o.d. Eltrombopag 50 mg o.d. Eltrombopag 75 mg o.d.	Placebo o.d.	Subjects with chronic ITP who had relapsed or were refractory to ≥ 1 prior ITP therapies	GlaxoSmithKline group 2007a[41]; Bussel 2007[40]
TRA 100773B[42]	Eltrombopag 50† mg o.d.	Placebo o.d.	Subjects with chronic ITP who had relapsed or were refractory to ≥ 1 prior ITP therapies	GlaxoSmithKline group 2007b[43]; Bussel 2009[42]
TRA 102537 RAISE[38;39]	Eltrombopag 50† mg o.d.	Placebo o.d.	Subjects with chronic ITP who had received ≥ 1 prior ITP therapies	GlaxoSmithKline group 2009[39]; Cheng 2011[38]
Tomiyama ASH 2009[48]	Eltrombopag 12.5† mg o.d.	Placebo o.d.	Previously treated Japanese subjects with chronic ITP and platelet counts <30 $X10^9$/L	Tomiyama ASH 2009, abs. no. 1324[48]

† starting dose; o.d. once daily; ASH American Society of Hematology, ITP: immune thrombocytopenia

5.2.5 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

Tomiyama 2009 is a conference abstract from the American Society of Hematology's (ASH) 2009 meeting[48]. It focuses solely on eltrombopag dose finding in a Japanese population. The study had a lower starting dose of eltrombopag at 12.5mg and a maximum dose of 50mg/day. By week six 60% of patients were responding to treatment with ≤25mg/day eltrombopag. The eltrombopag SPC[3] recommends a starting dose of 25mg for patients of South East Asian origin, compared to a starting dose of 50mg for Caucasian patients (median dose over 6 months in RAISE: 58mg/day). This study was excluded as the results for a Japanese population were thought to have limited relevance to the UK decision problem.

5.2.6 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 5.8 and key details should be presented in a table; the following is a suggested format.

A complete list of relevant non-RCT eltrombopag studies is included in Table B7. Only one full paper publication was available. Six relevant conference abstracts were also identified.

Table B7 List of relevant non-RCTs

Trial no.	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
TRA 108057 REPEAT[49]	Eltrombopag 50 mg in 3 cycles of repeated intermittent dosing	Subjects with previously treated ITP, who had platelet counts ≥ 20 $X10^9$/L and ≤ 50 $X10^9$/L and who had received ≥ 1 prior ITP therapies	To evaluate the effect of intermittent eltrombopag dosing	TRA 108057 REPEAT	Evaluates the effect of eltrombopag on platelet counts when administered during 3 cycles of repeated intermittent dosing
TRA 105325 EXTEND[44-46]	Eltrombopag 50† mg o.d. (see appendix 6 for algorithm)	Subjects previously enrolled in an ITP study of eltrombopag who completed treatment and follow-up periods	To evaluate the long term effects of eltrombopag	TRA 105325 EXTEND	Evaluates the safety and tolerability of eltrombopag for the long-term treatment of subjects with chronic ITP
Meyer 2011[50]	Eltrombopag 25 – 75 mg o.d. Romiplostim 1 – 7 µg/kg weekly	Subjects with chronic ITP who had received ≥1 prior treatment, and had platelet counts <10 $X10^9$/L	To assess infection related loss of platelet response during treatment with TPO-RAs	Meyer 2011	Evaluates the effect of infection related loss of response when treated with eltrombopag
Kuter ASH 2011[51]	Eltrombopag and Romiplostim	Patients >18yrs, with chronic ITP and a medical history for at least 12 months who have been treated with a TPO-RA for 4 weeks	To understand how TPO-RAs impact lives of chronic ITP patients, and the treatment decisions around the use of such agents	Kuter ASH 2011	Evaluates the impact of eltrombopag and romiplostim on a patient's quality of life according to the SF-36. Interim results.
Haselboeck ASH 2011[52]	Eltrombopag and Steroids	Not reported	To assess the function of platelets following eltrombopag treatment compared to steroid treatment and no treatment	Haselboeck ASH 2011	Provides some details of eltrombopag induced platelet response compared to steroid induced platelet response
Cooper ASH 2011[53]	Eltrombopag regimens according to TRA100773A and B, TRA102537 RAISE, TRA108057 REPEAT and TRA105325 EXTEND	Populations reported in eltrombopag trials listed in interventions	Assessment of the potential increased risk of cataracts associated with eltrombopag treatment	Cooper ASH 2011	Post hoc analysis of eltrombopag trials with a focus on the increased risk of cataract associated with eltrombopag.

Trial no.	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
Olney ASH 2011[54]	Eltrombopag regimens according to TRA100773A and B, TRA102537 RAISE, TRA108057 REPEAT and TRA105325 EXTEND	Adults with ITP in the trials listed in the interventions	Assessment of the safety and efficacy of eltrombopag in patients ≥65 years	Olney ASH 2011	Subgroup analysis of eltrombopag trials focusing on the elderly population

5.3 Summary of methodology of relevant RCTs

5.3.1 Information on the RCTs.

Methods

5.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

The methodology of the included eltrombopag RCTs is provided in Table B8. The three studies are all international, double-blind, randomised controlled trials assessing the efficacy of eltrombopag compared to placebo. At the time each of these studies was conducted, each was the largest placebo-controlled study in chronic ITP. The three studies comprise the largest placebo-controlled RCT database for any agent studied in cITP.

Table B8 Comparative Summary of methodology of the RCTs

Trial no.	TRA 100773A[40]	TRA 100773B[42]	TRA 102537 RAISE[38;39]
Location	International (North America, Europe, Africa and Asia, 44 sites in 14 countries, 13 UK sites)	International (North and South America, Europe, Africa, Asia and Australia, 63 sites in 23 countries, 13 UK sites)	International (North and South America, Asia, Africa, Europe and Australasia: 75 sites in 23 countries, 9 UK sites)
Design	Phase II, randomised, double-blind, placebo-controlled, parallel group, dose finding	Phase III, randomised, double-blind, placebo-controlled	Phase III, randomised, double-blind, placebo-controlled
Duration of study	Treatment phase was 6 weeks	Treatment phase was 6 weeks	Treatment phase was 6 months.
Method of randomisation	Patients were randomly assigned in a 1:1:1:1 ratio to receive placebo, or 30, 50, or 75 mg eltrombopag o.d. Randomisation was stratified according to concomitant ITP medications, splenectomy, and baseline platelet count. Randomisation codes were set up using an in-house validated randomisation system (RANDALL); patients were randomised using a GSK interactive voice response system, Registration And Medication Ordering System (RAMOS)	Patients were randomly assigned 2:1 to receive standard of care and either eltrombopag 50 mg or placebo. Randomisation was stratified by splenectomy status, baseline concomitant ITP medications, and baseline platelet counts. Randomisation codes were set up using an in-house validated randomisation system (RANDALL); patients were randomised using a GSK interactive voice response system, Registration And Medication Ordering System (RAMOS)	Subjects were randomised 2:1, eltrombopag to placebo. Randomisation was stratified by splenectomy status, baseline use or non-use of ITP medication and baseline platelet count ≤ 15 $X10^9$/L or > 15 $X10^9$/L. Randomisation codes were set up using an in-house validated randomisation system (RANDALL); patients were randomised using a GSK interactive voice response system, Registration And Medication Ordering System (RAMOS)
Method of blinding (care provider, patient and outcome assessor)	The study was double-blind and treatment allocation was blinded to the subjects, the site staff and sponsor personnel. Blinding was maintained by use of matching placebo tablets. The investigator could un-blind a subject's treatment assignment only in the case of an emergency, when knowledge of the investigational product was essential for the clinical management or welfare of the subject.	The study was double-blind and treatment allocation was blinded to the subjects, the site staff and sponsor personnel. Blinding was maintained by use of matching placebo tablets. The investigator could un-blind a subject's treatment assignment only in the case of an emergency, when knowledge of the investigational product was essential for the clinical management or welfare of the subject.	The study was double-blind. 25 mg and 50 mg eltrombopag and matching placebo tablets were supplied. Subjects received 2 bottles of tablets and were instructed to take 1 tablet from each bottle. All subjects initiated with either 50 mg eltrombopag (1 bottle 50 mg tablets + 1 bottle placebo) or placebo (2 bottles placebo). Dose adjustments by 25 mg were allowed whilst maintaining blinding; subjects returned both bottles and were dispensed 2 new bottles The investigator could un-blind a subject's treatment assignment only in the case of an emergency, when

Trial no.	TRA 100773A[40]	TRA 100773B[42]	TRA 102537 RAISE[38;39]
			knowledge of the investigational product was essential for the clinical management or welfare of the subject.
Intervention	Eltrombopag 30 mg (n = 29) Eltrombopag 50 mg (n = 27) Eltrombopag 75 mg (n = 26) Subjects who attained a platelet count > 200X10^9/L discontinued treatment, but continued in the study.	Eltrombopag 50† mg (n = 74) Dose increase to 75mg permitted after 3 weeks if platelet count remained <50X10^9/L. Treatment discontinued if platelet count >200 X10^9/L was attained, but they continued in the study.	Eltrombopag 50† mg (n = 135) The dose of study medication was adjusted based on individual platelet counts; dose increase up to maximum of 75mg allowed after 22 days if platelet count was <50X10^9/L. Dose decreases to a minimum of 25mg required if platelet count was >200X10^9/L. If platelet count was >400X10^9/L dose was interrupted and resumed at the next lowest dose once platelet count fell <150X10^9/L. After 6 weeks on study, if patients had platelet count of >100X10^9/L for 2 consecutive weeks, reduction in concomitant therapy was permitted.
Comparator	Placebo (n = 27)	Placebo (n = 38)	Placebo (n = 62)
Primary outcomes	The proportion of responders, defined as patients who had an increase in platelet count to ≥ 50X10^9/L at day 43 of the study. Subjects withdrawn early due to platelet count exceeding 200 X10^9/L, were still considered responders	The proportion of responders, defined as patients who had an increase in platelet count to ≥ 50X10^9/L at day 43 of the study. Subjects withdrawn early due to platelet count exceeding 200 X10^9/L, were still considered responders	The odds of achieving a platelet count ≥ 50 X10^9/L and ≤ 400X10^9/L during the 6-month treatment period
Secondary outcomes	• Incidence and severity of bleeding, assessed at every visit according to the WHO bleeding scale; grade 0, no bleeding; grade 1, petechiae; grade 2, mild blood loss; grade 3, gross blood loss; grade 4, debilitating blood loss • Outcomes of subjects incurring a haemostatic challenge (collected retrospectively) • Serum thrombopoietin level,	• Odds of responding to treatment, i.e. a shift from a baseline platelet count < 30 X10^9/L to a platelet count of ≥ 50 X10^9/L during weeks 2–6 • The proportion of subjects with platelet counts ≥ 50 X10^9/L and at least x2 the baseline at day 43 • Incidence and severity of bleeding, assessed at every visit according to the WHO bleeding scale • Outcomes of subjects incurring a	• Proportion of subjects receiving a rescue treatment (defined as a composite of: new ITP medication, increased dose of a concomitant ITP medication from baseline, platelet transfusion, and/or splenectomy) during the 6-month treatment period • Proportion of subjects with at least 75% of their assessments ≥ 50X10^9/L and ≤ 400X10^9/L • Maximum duration of response, as per primary outcome, for each subject, both continuous and cumulative (weeks) • Proportion of subjects achieving a platelet count of

Trial no.	TRA 100773A[40]	TRA 100773B[42]	TRA 102537 RAISE[38;39]
	measured by enzyme-linked immunosorbent assay • HRQoL, measured using the SF-36v2 tool • Safety and tolerability	haemostatic challenge • HR-QoL, measured using the SF-36v2 tool • Safety and tolerability	≥ 50 $X10^9$/L and ≤ 400$X10^9$/L during weeks 2–6 of study treatment • Proportion of subjects with a reduction in use of concomitant ITP medications from baseline • Incidence and severity of symptoms associated with ITP, including bleeding, bruising, petechiae, measured using the WHO bleeding scale and ITP bleeding score • HR-QoL assessments included SF-36v2, FACT-Th subscale, the FACIT-fatigue subscale and the MEI-SF score. • Safety and tolerability (including: adverse events graded according to the NCI CTCAE v3.0; serious adverse events; ECG; ocular examinations; clinical laboratory evaluations; renal and liver function monitoring)
Duration of follow-up	Subjects were assessed every 2 weeks for up to 6 weeks after discontinuation of study drug	Subjects were assessed at 1, 2, 4 and 6 weeks after discontinuation of study drug	After discontinuation of study drug, subjects were followed-up at 1, 2 and 4 weeks then at 3 and 6 months.

† starting dose: o.d. once daily; ITP immune thrombocytopenia HR-QoL, health-related quality of life; WHO, World Health Organisation; MEI-SF, Motivation and Energy Inventory Short Form; FACIT, functional assessment of chronic illness therapy; FACT-Th, functional assessment of cancer therapy thrombocytopenia, NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events

Participants

5.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

The eligibility criteria for the included RCTs are provided in Table B9. The studies had near identical inclusion criteria and similar exclusion criteria as shown in Table B9.

Table B9 Eligibility criteria in the included RCTs

Trial no.	Inclusion criteria	Exclusion criteria
TRA 100773A[40]	• Aged ≥ 18 years • ≥ 6-month history of ITP • Received ≥ 1 previous treatments for ITP • Had a platelet count of < $30X10^9$/L at enrolment • Patients receiving maintenance immunosuppressive regimens eligible if the dose had been stable for ≥ 1 month • Values within the normal range for neutrophils, reticulocyte count, creatinine, and liver enzymes	• Secondary immune thrombocytopenia • Haemoglobin levels < 10 g/dL • Congestive heart failure, arrhythmia or thrombosis within the previous year • Myocardial infarction within the previous 3 months • Pregnant or lactating women
TRA 100773B[42]	• Aged ≥ 18 years • ≥ 6-month history of ITP • Received ≥ 1 previous treatments for ITP • Had a platelet count of < $30X10^9$/L at enrolment • Patients could receive other ITP drugs as maintenance therapy if the dose had been stable for ≥ 1 month and were intended to remain stable throughout the treatment period • Normal creatinine and liver enzyme concentrations	• Evidence of HIV, or hepatitis C or B infections • Congestive heart failure, arrhythmia or thrombosis within the previous year • Myocardial infarction within the previous 3 months • Pregnant or lactating women • Patients who required use of drugs containing calcium or magnesium
TRA 102537 RAISE[38;39]	• Aged ≥ 18 years • Chronic ITP • Had a platelet count of < $30X10^9$/L at enrolment • Received ≥ 1 prior ITP therapies • Responded to a previous ITP therapy or have had a bone marrow examination consistent with ITP within 3 years • Patients treated with concomitant ITP medication eligible if the dose had been stable for ≥ 1 month • Creatinine and liver enzyme concentrations not to exceed upper limit of normal by more than 20%	• Concurrent malignant disease and/or history of treatment with cytotoxic chemotherapy/radiotherapy • History of arterial or venous thrombosis in the presence of ≥ 2 risk factors for thromboembolic events (e.g. smoking, diabetes, hypercholesterolaemia or hereditary thrombophilic disorders) • Secondary immune thrombocytopenia • Pre-existing cardiovascular disease or arrhythmia • Pregnant or lactating women • Previous participation in a clinical trial of eltrombopag

5.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Full details of the baseline characteristics across the three included trials are provided in Table B10 and Table B11.

The baseline characteristics across the three trials were similar, with median age 48 - 50 years, proportion of females 61- 69%, and white ethnicity 74 - 79%. All were stratified by splenectomy status (36-47% splenectomised), concomitant ITP medication (present in 32-48%) and platelet count ≤15X10^{9}/L (48-49% of patients). TRA 100773A[41], TRA 100773B[42] and TRA 102537 (RAISE)[38;39] reported that 26%, 20% and 23% of patients, respectively, had received 5 or more prior ITP treatments.

Table B10 Characteristics of participants in TRA 100773A[40] and TRA 100773B[42] across randomised groups

Trial No.	TRA 100773A[40]						TRA 100773B[42]		
Patient Characteristic	**Placebo (n=29)**	**Eltrombopag 30 mg (n=30)**	**Eltrombopag 50mg (n=30)**	**Eltrombopag 75 mg (n=28)**	**Total (n=117)**	**p-value**	**Placebo (n=38)**	**Eltrombopag (n=76)**	**Total (n=114)**
Age (year)						0.04†‡			
Median	42	51	45	54.5	50		51	47	48
Range	18–85	23–79	23–81	18–85	18–85		21–79	19–84	19–84
Mean (SD)							48 (16)	51 (17)	50 (17)
Gender – no. (%)						0.33§			
Female	16 (55)	16 (53)	21 (70)	20 (71)	73 (62)		27 (71)	43 (57)	70 (61)
Male	13 (45)	14 (47)	9 (30)	8 (29)	44 (38)		11 (29)	33 (43)	44 (39)
Race						0.02†‡§¶			
Black	1 (3)	1 (3)	-	-	2 (2)		0	1 (1)	1 (< 1)
Asian	2 (7)	4 (13)	12 (40)	3 (11)	21 (18)		8 (22)-	12 (16)-	20 (17)-
White	25 (86)	25 (83)	18 (60)	25 (89)	93 (80)		26 (69)	58 (77)	84 (74)
Mixed	1 (3)	-	-	-	1 (< 1)		2 (5)-	1 (1)-	3 (3)-
Other	-	-	-	-	-		2 (5)	4 (5)	6 (5)
Stratification Variables:									
Splenectomy	14 (48)	15 (50)	15 (50)	11 (39)	55 (47)	0.82§	14 (37)	31 (41)	45 (39)
Concomitant ITP medication	6 (21)	10 (33)	12 (40)	10 (36)	38 (32)	0.43§	17 (45)	32 (42)	49 (43)
Platelet ≤15 $X10^9$/L	14 (48)	15 (50)	12 (40)	15 (54)	56 (48)	0.82§	17 (45)	38 (50)	55 (48)
Prior Treatments – n (%)						0.52§*			
≥ 1	28 (97)	29 (97)	30 (100)	26 (93)	113 (97)		38 (100)	76 (100)	114 (100)
≥ 2	21 (72)	26 (87)	24 (80)	16 (57)	87 (74)		26 (68)	56 (74)	82 (72)
≥ 3	14 (48)	17 (57)	18 (60)	11 (39)	60 (51)		16 (42)	42 (55)	58 (51)
≥ 4	12 (41)	12 (40)	12 (40)	6 (21)	42 (36)		9 (24)	30 (39)	39 (34)
≥ 5	8 (28)	7 (23)	10 (33)	5 (18)	30 (26)		7 (18)	16 (21)	23 (20)

†Kruskall-Wallis test across all treatment groups; ‡ significant at 5% level (two-sided); ¶ white/non-white comparison; § based on chi-squared test across all groups; *patients with≥1 prior therapy

Table B11 Characteristics of participants in TRA 102537 RAISE across randomised groups[38;39]

Characteristic	Placebo (N = 62)	Eltrombopag 50 mg (N= 135)	Total (N = 197)
Age – year			
Median	52.5	47.0	48.0
Range	18–77	18–85	18–85
Sex – no. (%)			
Female	43 (69)	93 (69)	136 (69)
Male	19 (31)	42 (31)	61 (31)
Race – no. (%)			
African American	1 (2)	2 (1)	3 (2)
American Indian/Alaska native	4 (6)	8 (6)	12 (6)
Asian	13 (21)	21 (16)	34 (17)
Native Hawaiian/Pacific islander	0	1 (< 1)	1 (<1)
White	44 (71)	101 (75)	145 (74)
Mixed	0	2 (1)	2 (1)
Stratification variables – no. (%)			
Splenectomy	21 (34)	50 (37)	71 (36)
Concomitant ITP medication	31 (50)	63 (47)	94 (48)
Platelets ≤ 15 $X10^9$/L†	30 (48)	67 (50)	97 (49)
Median platelet count ($X10^9$/L)	16 (9-24)	16 (8-22)	16 (8-24)
Prior therapies			
≥ 1	62 (100)	135 (100)	197 (100)
≥ 2	50 (81)	105 (78)	155 (79)
≥ 3	32 (52)	75 (56)	107 (54)
≥ 4	20 (32)	51 (38)	71 (36)
≥ 5	11 (18)	35 (26)	46 (23)

†One subject (placebo group) had a missing baseline platelet count

Outcomes

5.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

The primary and secondary outcomes of the included eltrombopag studies are provided in Table B12, along with a discussion of the validity of the outcome measures.

The primary outcome of the TRA 100773A and B trials was platelet response defined as a platelet count of ≥50 $X10^9$/L on day 43, the last day of the treatment period[40;42]. The primary outcome of RAISE was the odds of achieving a platelet response of ≥50 - ≤400 $X10^9$/L at any point during the 6 month treatment period[38;39]. Platelet counts between 50 and 400x10 $X10^9$/L were not considered responses if achieved during the administration of rescue treatment, and until platelets had fallen below 50 $X10^9$/L following rescue treatment discontinuation. The trials reported a variety of secondary outcomes.

Bleeds were reported using the World Health Organization (WHO) scale, and the ITP bleeding scale (see Appendix 2 for details). The WHO bleeding scale[55] is a reliable and widely used measure of bleeding symptoms.The ITP bleeding scale provides a more specific indication of bleeding severity according to location of bleeding (note: due to limited reporting, the ITP bleeding scale results were not reported in Cheng 2011 (they are available in the CSR)).

Table B12 Primary and secondary outcomes of the RCTs

Trial no.	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
TRA 100773A[40]	The proportion of responders, defined as patients who had an increase in platelet count to ≥ 50X10^9/L at day 43 of the study. Subjects withdrawn early due to platelet count exceeding 200 X10^9/L, were still considered responders	The fundamental goal for treatment is to achieve a platelet count that prevents major bleeds rather than "normalising" the platelet count[10]. Platelet count is accepted as a surrogate measure for clinical outcomes (The American Society of Hematology ITP Practice Guideline Panel, 1997); it is objective, clinically relevant and easily compared. The relationship between platelet level, bleeding rates and bleeding severity has been recently demonstrated by Gernsheimer (2010).[18]	Incidence and severity of bleeding, assessed at every visit according to the WHO and ITP bleeding scales † Outcomes of subjects incurring a haemostatic challenge (collected retrospectively) Serum thrombopoietin level, measured by enzyme-linked immunosorbent assay HR-QoL, measured using the SF-36v2 tool Safety and tolerability	The WHO bleeding scale[55] is a reliable and widely used measure of bleeding symptoms. TRA 100773A, TRA 100773B and TRA 102537 RAISE report bleeding using the WHO scale. The ITP bleeding score[56] is a relatively new scale that provides a more specific indication of bleeding severity according to location. There is no widely used, uniformly accepted and validated tool to evaluate health outcomes in adult ITP. The SF-36 instrument is a validated, well respected and widely used global measure of health-related quality of life[57] and its reliability has been confirmed in ITP[25]. FACIT-fatigue assesses the severity and impact of fatigue on daily activities. The thrombocytopenia subscale of FACT (FACT-Th) was used to further frame the impact of thrombocytopenia on daily activities and mental health [58;59] The National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (NCI CTCAE) is a descriptive terminology that is well accepted and widely used for recording the severity of adverse events.
TRA 100773B[42]	The proportion of responders, defined as patients who had an increase in platelet count to ≥ 50X10^9/L at day 43 of the study. Subjects withdrawn early due to platelet count exceeding 200 X10^9/L, were still considered responders		Odds of responding to treatment, i.e. a shift from a baseline platelet count < 30X10^9/L to a platelet count of ≥ 50 X10^9/L during weeks 2–6 The proportion of subjects with platelet counts ≥ 50X10^9/L and at least x2 the baseline amount at 43 days Incidence and severity of bleeding, assessed weekly during treatment and at 1, 2, 4 and 6 weeks post treatment, according to the WHO bleeding scale† Outcomes of subjects incurring a haemostatic challenge HR-QoL, measured using the SF-36v2 tool Safety and tolerability	

Trial no.	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
TRA 102537 RAISE[38;39]	The odds of achieving a platelet count ≥ $50X10^9$/L and ≤ $400X10^9$/L during the 6-month treatment period		Proportion of subjects receiving a rescue treatment (defined as a composite of: new ITP medication, increased dose of a concomitant ITP medication from baseline, platelet transfusion, and/or splenectomy) during the 6-month treatment period Proportion of subjects with at least 75% of their assessments ≥ $50X10^9$/L and ≤ $400X10^9$/L Maximum duration of response for each subject Proportion of subjects achieving a platelet count of ≥ $50X10^9$/L and ≤ $400X10^9$/L during weeks 2–6 of study treatment Proportion of subjects with a reduction in use of concomitant ITP medications from baseline Incidence and severity of symptoms associated with ITP, including bleeding, bruising, petechiae, measured using the WHO bleeding scale† and ITP bleeding score HR-QoL assessments included SF-36v2, FACT-Th subscale, the FACIT-fatigue subscale. Outcomes of subjects incurring a haemostatic challenge Safety and tolerability (including: adverse events graded according to the NCI CTCAE v3.0; serious adverse events; ECG; ocular examinations; clinical laboratory evaluations; renal and liver function monitoring)	

†WHO bleeding scale and ITP bleeding scale defined in Appendix 2; 4: HR-QoL, health-related quality of life; WHO, World Health Organisation; MEI-SF, Motivation and Energy Inventory Short Form; FACIT, functional assessment of chronic illness therapy; FACT-Th, functional assessment of cancer therapy thrombocytopenia, NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events

Statistical analysis and definition of study groups

5.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT

Details of the statistical analysis performed in each of the included eltrombopag trials are provided in Table B13.

Table B13 Summary of statistical analysis in the RCTs

Trial no.	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
TRA 100773A[40]	Global null hypothesis: The odds of response were equal across all 4 study groups	The efficacy population was the primary population for efficacy analyses and comprised all randomised subjects treated with ≥ 1 dose of study medication, who had a baseline platelet count of < $30X10^9$/L A logistic-regression model (adjusted for: use or non-use of concomitant ITP medication, splenectomy status, and baseline platelet count) was used to test the global null hypothesis. If the null hypothesis was rejected, the odds of a response in each eltrombopag group were compared with the odds of a response in the placebo group by means of a closed testing procedure to maintain the overall type 1 error at 2.5% (1-sided). The interactions between treatment response and stratification variables were evaluated at the 10% level of significance Two interim analyses were planned when data were available for 1/3 and 2/3 of the maximum intended sample size of 272 patients. At the first interim analysis a given dose of eltrombopag could be stopped for reasons of efficacy (1-sided P ≤ 0.0113), futility (1-sided P ≥ 0.333), or safety. In the first interim analysis, involving data from 104 patients, the groups receiving the two highest doses of eltrombopag met the predefined stopping criteria for efficacy under the closed testing procedure. The group receiving 30 mg of eltrombopag did not meet the stopping criterion for either efficacy or futility (2-sided P = 0.340); however, this dose was not continued because of high response rates for doses of 50 mg and 75 mg and a similar incidence of adverse events among patients in all four study groups. After the decision was made to stop the	Two interim analyses were planned when data were available for 1/3 and 2/3 of the maximum intended sample size of 272 patients (68 per group). The trial had a 90% statistical power at the 2.5% level of significance (1-sided) to detect a 30% difference in the proportion of patients with a response to patients without a response between the placebo group and each eltrombopag group, assuming that 30% of patients receiving placebo would have a response	For patients who withdrew prematurely because of a platelet count of more than $200X10^9$/L, the LOCF imputation was applied. Patients who withdrew prematurely for any other reason were counted as not having had a response

Trial no.	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		study, the final analysis involving data from 118 patients, including 14 patients who enrolled after the interim cut-off date, was performed		
TRA 100773B[42]	The study was powered to compare the odds of response on day 43 of the study between the placebo and eltrombopag groups; however additional participants were included to inform the safety analysis.	The efficacy population was the primary population for efficacy analyses and comprised all randomised subjects treated with ≥ 1 dose of study medication, who had a baseline platelet count of < $30X10^9$/L The odds of a response were compared between eltrombopag and placebo treatment groups using a logistic regression model adjusted for ITP medication use at randomisation, splenectomy status and baseline platelet count. The overall type I error was no more than 5% (2-sided)	On the basis of results from the phase II study (TRA100773A), it was estimated that 25% and 60% of patients would respond to placebo and eltrombopag, respectively. To provide 90% power at the 5% level of significance (2-sided) 87 evaluable patients (58 eltrombopag and 29 placebo) were required. However, to provide supplementary safety data, additional patients were recruited for a total of 114 patients (76 patients randomly assigned to eltrombopag and 38 to placebo)	For patients who withdrew prematurely because of a platelet count of more than $200X10^9$/L, the LOCF imputation was applied and subjects were classified as responders Subjects were classified as non-responders if they discontinued treatment prior to the day 43 visit for any reason other than a platelet count >$200\ X10^9$/L, irrespective of their last on treatment platelet count
TRA 102537 RAISE[38;39]	The study was powered to compare the odds of response at any point during the 6 months of the study between the placebo and eltrombopag groups; however additional participants were included to inform the safety analysis.	All efficacy analyses were carried out on the ITT population The relative difference between eltrombopag and placebo with respect to the odds of achieving a platelet count ≥ 50 and ≤ 400 $X10^9$/L during 6 months of treatment was assessed using a repeated measures model for binary data using generalised estimating equations methodology. The comparison was made at the 1% (2-sided) level of significance A logistic regression model adjusted for the randomisation stratification variables was used to	Assuming 60% and 25% positive response rates in the eltrombopag and placebo groups, respectively, 120 evaluable subjects were required to provide ≥ 90% power at the 1% (2-sided) level of significance. To ensure sufficient power for both the primary and main secondary endpoints, a 30% increase in subjects was pre-	There were no imputations for intermittent missing data in the primary analysis data set. If a subject did not have an evaluation at a nominal visit (defined as weeks 1 to 6 inclusive, week 10 and every 4 weeks thereafter) due to receiving a dose adjustment, information from the immediately preceding non-nominal visit was used as long as the subject had

Trial no.	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		compare the proportion of subjects who achieved platelet counts of ≥ 50 $X10^9$/L and ≤ 400 $X10^9$/L for at least 75% or more of their assessments, the proportion of subjects with a reduction in concomitant ITP medication use and the proportion of subjects who received a rescue treatment	specified to compensate for potential missing data and drop-outs during the full 6 month study duration, to give a total of 189 subjects (63 placebo and 126 eltrombopag)	not withdrawn from the study. All other intermittent missing data remained as missing in all analyses. Evaluations for a subject who withdrew from the study were classified as a negative response from the time of withdrawal and for subsequent visits

ITT, intention-to-treat; LOCF, last observation carried forward

5.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

TRA 100773A[40]

1. A difference in response to eltrombopag relative to placebo was assessed for the following subgroups: splenectomy status, age (categorized as 18-49 years inclusive, 50-64 years inclusive and ≥65 years), race (white vs. nonwhite), concomitant ITP medications at baseline (yes vs no) and baseline platelet count of more than vs less or equal to $15X10^9$/L. (pre-planned).

TRA 100773B[42]:

1. A difference in response to eltrombopag relative to placebo was assessed for the following subgroups: splenectomy status, concomitant ITP medications at baseline (yes vs no) and baseline platelet count of more than vs less or equal to $15X10^9$/L. (pre-planned).
2. Post-hoc analyses were performed on the following subgroups: number of prior ITP therapies (1, 2, 3, 4, >4), age (categorized as 18-49 years inclusive, 50-64 years inclusive and ≥65 years) and sex.

TRA 102537 RAISE[38;39]:

1. A difference in response to eltrombopag relative to placebo was assessed for each stratification factor (splenectomy status, concomitant medication use and baseline platelet count) as well as the following subgroups: sex, race[1] (categorized as White, Asian, African American and Other) and age (categorized as 18-49 years inclusive, 50-64 years inclusive, 65-74 years inclusive and ≥75 years). This was done for the primary efficacy and main secondary efficacy endpoints.The level of significance for all interactions was set to 10%. If a significant interaction was seen, the analysis model was repeated for each level of the strata/subgroup. (pre-planned).
2. Analysis of the primary endpoint by weight subgroups (post-hoc).
3. Analysis of steroid induced side effects in patients receiving concomitant medications at baseline (post-hoc).

Participant flow

5.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Details of patient disposition in each of the included eltrombopag trials are provided in Figure B5, Figure B6 and Figure B7.

[1] Differences across prespecified racial categories could not be assessed due to low numbers of subjects in the African American category.

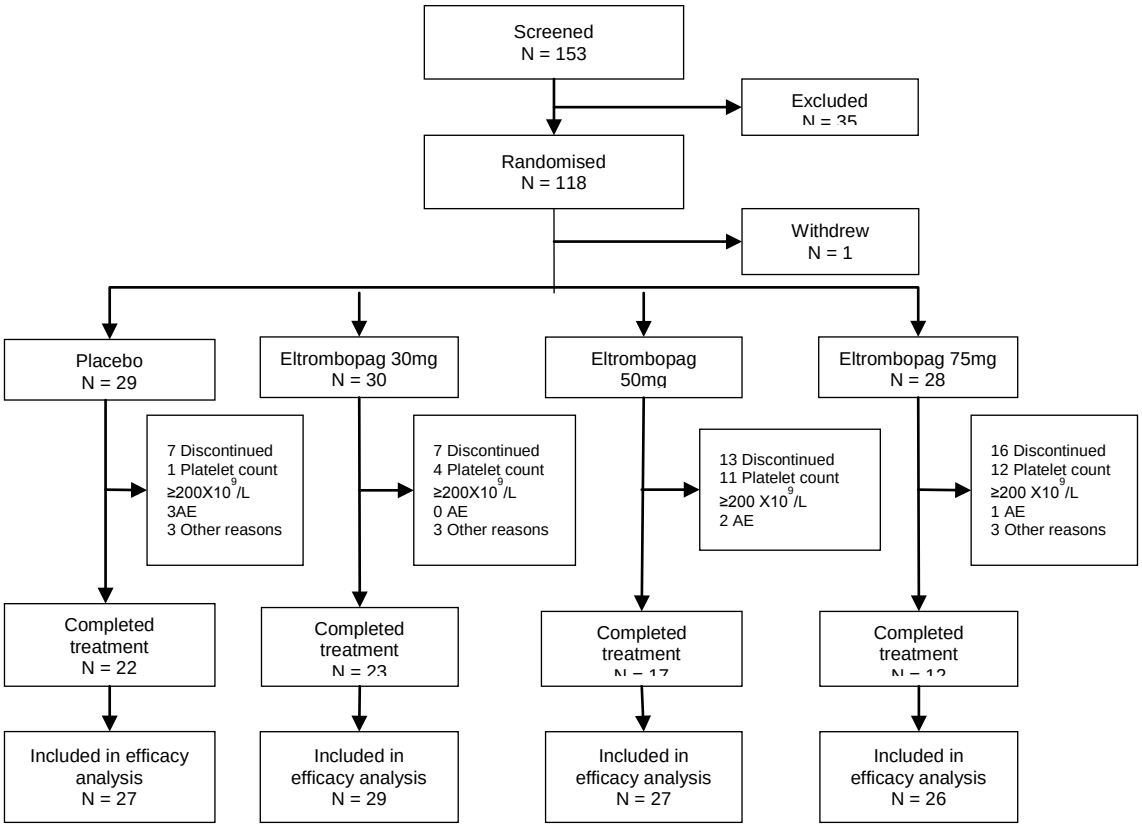


Figure B5 CONSORT diagram of TRA 100773A

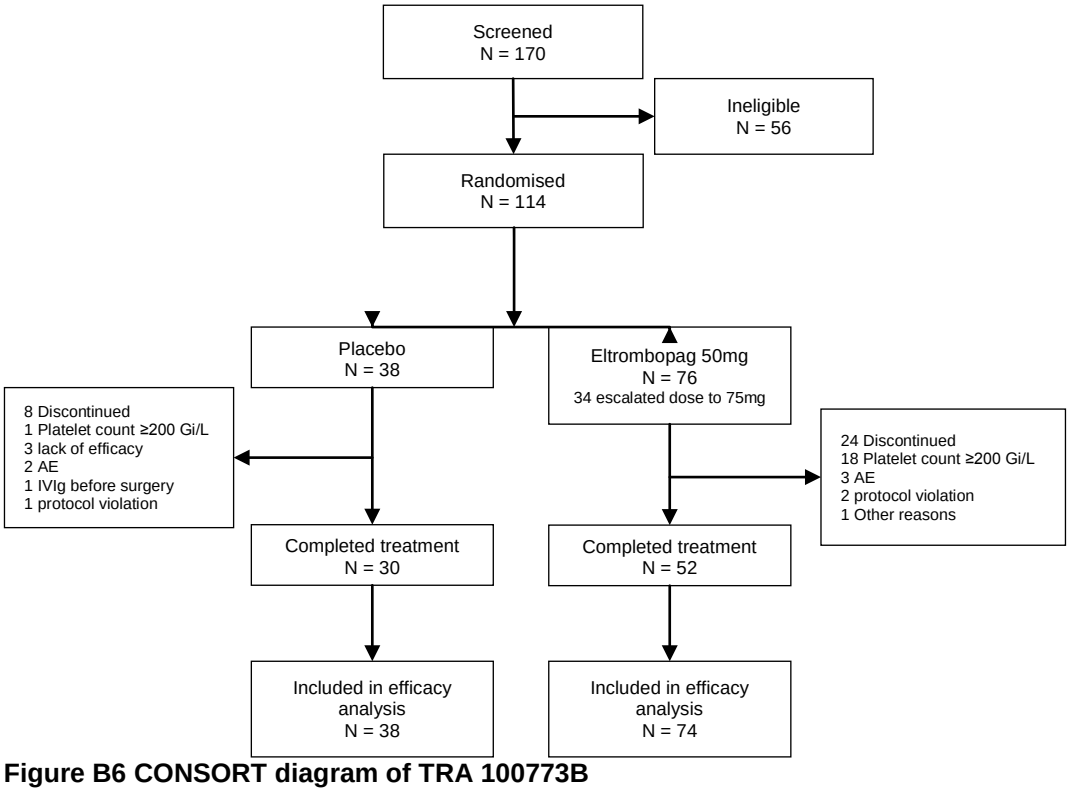


Figure B6 CONSORT diagram of TRA 100773B

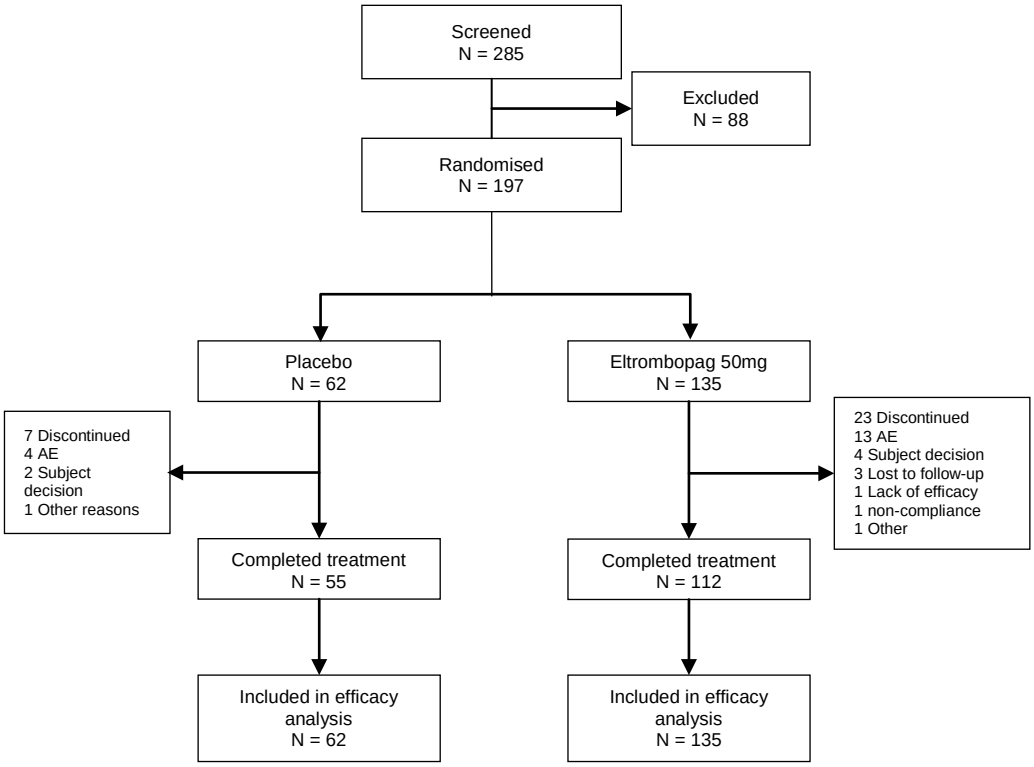


Figure B7 CONSORT diagram of TRA 102537 RAISE

5.4 Critical appraisal of relevant RCTs

The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG.

The TRA 100773A[40], TRA 100773B[42] and RAISE[38;39] trials are the three eltrombopag studies included in this appraisal. All are reported as full publications.
All three studies were randomised, double-blind, placebo controlled trials. Patients were stratified by splenectomy status, use of concomitant ITP medication and platelet count at baseline (>/≤15X10^9/L) before randomisation. Randomisation codes were set up using an in-house validated randomisation system (RANDALL); patients were randomised using a GSK interactive voice response system, Registration And Medication Ordering System (RAMOS). Thus, both randomisation and allocation concealment were adequate. Double-blinding was maintained by the use of identical eltrombopag and placebo tablets, and could only be broken in the case of a medical emergency. The definition of medical emergency was not provided. Patient disposition was reported according to CONSORT guidelines, and reasons for withdrawals were given. No imbalance was observed in the drop-out rates between the arms. TRA 100773A and TRA 10773B reported outcomes of the efficacy population while RAISE reported outcomes of the intention-to-treat population.
A complete quality assessment of the three individual trials is provided in Appendix 3
A summary of the quality assessments is given in Table B14.

Table B14 Quality assessment of included eltrombopag RCTs

Trial no.	TRA 100773A[40]	TRA 100773B[42]	TRA 102537 RAISE[38;39]
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes but reported outcomes from the efficacy population Yes	Yes but reported outcomes from the efficacy population Yes	Yes Yes

5.5 Results of the relevant RCTs

5.5.1 Results of TRA 100773A[40;41]

Primary efficacy results

The primary end point was an increase in platelet count to ≥50 $X10^9$/L on day 43 of dosing. At the 50 mg and 75 mg doses respectively, 70.4% and 80.8% of patients met the response end point, and the trial was stopped at the first interim analysis. The analysis of responders is shown in Table B15.

Table B15 Analysis of responders in TRA 100773A

	TRA 100773A			
	Placebo (n=27)	Eltrombopag		
		30mg (n=29)	50mg (n=27)	75mg (n=26)
Evaluable	27	29	27	26
Responders, n (%)	3 (11.1)	8 (27.6)	19 (70.4)	21 (80.8)
OR (active relative to placebo) [1]	NA	3.09	21.96	38.82
95% CI	NA	0.69, 13.75	4.72, 102.23	7.62, 197.73
p-value (1-sided)	NA	0.070	< 0.001	< 0.001

OR: Odds Ratio; CI: Confidence Interval [1]: logistic regression analysis adjusted for immunosuppressant use, splenectomy, baseline platelet counts < 15x109/L and treatment

Subgroup analysis

Further analyses showed no significant interaction between a response and prior splenectomy, age or race (white vs nonwhite). In all groups except those receiving 75mg of eltrombopag, there was a higher percentage of responders among patients using concomitant ITP medication. Among patients who had a baseline platelet count of more than $15x10^9$/L, there was a substantially higher percentage of responders in all groups except for the group receiving 30mg of eltrombopag (in which the overall percentage of responders was lowest) (two-sided P=0.093 for patients taking concomitant ITP medications and P=0.042 for patients with a baseline platelet count more than $15x10^9$/L).

Incidence and severity of bleeding

In the 30mg, 50mg and 75mg groups, the incidence and severity of bleeding decreased compared to baseline as the platelet count increased during the on-therapy period. The proportion of patients with bleeding, was lower in all eltrombopag treatment groups compared to placebo from day 15 to day 43 of treatment. Over the 6 week follow-up, as platelet counts returned to near-baseline levels, so did the incidence of bleeding.

Haemostatic challenge

In this study a total of four patients faced situations typically associated with increased risk of bleeding, herein denominated as haemostatic challenges. One, in the placebo group, required treatment with IVIg prior to undergoing surgery. The remaining three, all in the 50mg eltrombopag group, did not require any rescue treatments (two underwent surgery and one was involved in a car accident).

Health related quality of life (HRQoL)

HRQoL was assessed using the physical and mental component scores of the SF36 v2 survey. Individual dimension scores remained similar to baseline at the end of the

study. The only statistically significant change from baseline was a decrease in the emotional-role score in the 75mg eltrombopag group (p=0.02).

5.5.2 Results of TRA 100773B[42;43]

Primary efficacy results

The primary endpoint for TRA 100773B was response as measured by a platelet count increase to ≥50 $X10^9$/L on day 43 of dosing. This was achieved by 59% of the eltrombopag group and 16% of the placebo group. The analysis of responders is shown in Table B16.

Table B16 Analysis of responders in TRA 100773B

	Placebo (n=38)	Eltrombopag (n=74)
Evaluable	37	73
Responders, n (%)	6 (16.2)	43 (58.9)
OR (active relative to placebo)	NA	9.61
95% CI	NA	3.31, 27.86
p-value (2-sided)	NA	< 0.001

OR: Odds Ratio; CI: Confidence Interval

Subgroup analysis

Response was also assessed according to the stratification variables (use of concomitant ITP medication at baseline, splenectomy status, and baseline platelet count less than or greater than 15 X109/L). None of these variables significantly affected response (Figure B8).

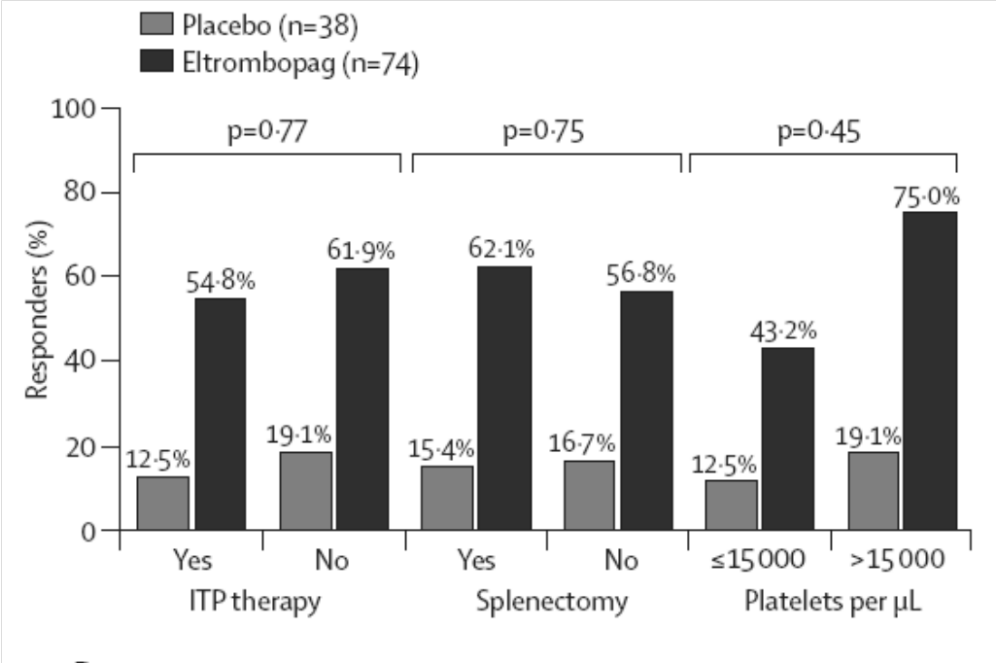


Figure B8 Percentage of responders according to baseline stratification variables in the TRA 100773B study (Efficacy population). p-values refer to the interaction between treatment group and stratification variable.

Other response endpoints

The odds of responding to eltrombopag between weeks 2 and 6 of treatment were significantly greater (OR = 8.79) than the odds of responding to placebo (Table B17).

Table B17 Odds of responding to treatment at any point between weeks 2 and 6 of the treatment period – TRA 100773B

	Eltrombopag relative to placebo
OR of responding at any point during treatment	8.79
95% CI	3.54, 21.86
p-value	< 0.0001

OR: odds ratio; CI: confidence interval

During the treatment period, 58% of patients treated with eltrombopag achieved platelet counts ≥ $50X10^9$/L and at least 2 times baseline, compared with 14% in the placebo group (p<0.001).

Risk of bleeding

The odds ratios for bleeding in the TRA 100773B study are presented in Table B18. At day 43 there was significantly lower risk of bleeding in the eltrombopag arm compared to placebo. Similarly, the eltrombopag arm was significantly less likely to suffer a bleed (WHO grades 1-4) at any point during treatment.

Table B18 Risk of bleeding in the TRA 100773B study

WHO G1-4 bleeding, day 43		Efficacy population
Evaluable, n	51	30
Patients experiencing bleeding, n (%)	20 (39)	18 (60)
OR		0.27
95% CI		0.09,0.88
p-value (two sided)		0.029
WHO G1-4 bleeding, any point during treatment		ITT population
Evaluable, n	76	38
Patients experiencing bleeding, n (%)	46 (61)	30 (79)
OR		0.49
95% CI		0.26,0.89
p-value (two sided)		0.021

OR: Odds Ratio, WHO: World Health Organisation, G: Grade; CI: Confidence Interval

Haemostatic challenge

In this study a total of three patients experienced haemostatic challenges. One patient in the eltrombopag group had a tooth extraction one week after treatment

discontinuation with no additional medication required. Two patients in the placebo group underwent surgery and received IVIg, platelet transfusion and tranexamic acid in preparation.

Health related quality of life (HRQoL)

HRQoL was assessed using the physical and mental component scores of the SF36 v2 survey. As in TRA 100773A, individual dimension scores were similar at baseline and end of study. The mean utility scores were comparable between responders and non-responders, with no significant differences observed from baseline.

Study medication and dose modifications

The starting dose of eltrombopag was 50mg/day. In the event of lack of response this could be increased to 75mg/day after day 22. Of the 74 patients who received eltrombopag and were included in the efficacy analysis, 40 received 50 mg only. Thirty-three patients achieved platelet counts ≥ 50X10^9/L, 18 of whom had platelet counts >200 X10^9/L. Thirty four patients required dose increases to 75mg, and 10 of those showed an increase in platelet count to ≥ 50 X10^9/L (none exceeding 200 X10^9/L). Six patients did not achieve platelet counts ≥ 50X10^9/L at 50 mg but did not increase their dose to 75 mg, and one patient was non-evaluable.

5.5.3 Results of TRA 102537 RAISE[38;39]

The RAISE study provides a six month analysis of the efficacy and safety of eltrombopag plus local standard of care compared to placebo plus local standard of care.

Primary efficacy results

The primary endpoint of RAISE was the odds of achieving a platelet count of between 50 and 400X10^9/L at any point during the six month treatment period, with eltrombopag versus placebo. The odds of responding to eltrombopag were approximately 8 times greater than the odds of responding to placebo (OR 8.2 [99% CI 3.59, 18.73, p <0.001 at the 1% level of significance], Table B19).

Table B19 Odds of response at any point during treatment (primary end point), TRA 102537 RAISE study (ITT population)

	Eltrombopag	Placebo
Evaluable, n	134	60
Responders, n (%)	106 (79)	17 (28)
OR of responding		8.2
99% CI		3.59, 18.73
p-value (2-sided versus. placebo)		< 0.001

OR: Odds Ratio; CI: Confidence Interval

Numbers of responders at different times during the study are shown in Table B20 and Figure B9. The proportion of responders in the eltrombopag group was between

37% (day 8) and 56% (day 36) for all nominal on-therapy visits. In comparison, the proportion of responders in the placebo group was between 7% (day 8) and 19% (week 22).

One week after discontinuation of treatment 42% of subjects treated with eltrombopag maintained platelet counts of 50-400 $X10^9$/L, compared to 15% in the placebo group. Two weeks after the end of treatment, the proportion of responders in the eltrombopag group returned to levels similar to the placebo group.

Table B20 Summary of responders, ITT population (TRA 102537 RAISE primary data set)

Timing of assessment	Placebo N = 62		Eltrombopag N = 135	
	Evaluable N	Responders n, (%)	Evaluable N	Responders n, (%)
Baseline	61	1 (2)	135	1 (1)
Day 8	60	4 (7)	134	50 (37)
Day 15	60	5 (8)	133	61 (46)
Day 22	59	5 (8)	133	68 (51)
Day 29	60	6 (10)	131	64 (49)
Day 36	60	5 (8)	134	75 (56)
Day 43	59	8 (14)	134	73 (54)
Week 10	47	8 (17)	108	56 (52)
Week 14	50	9 (18)	114	52 (46)
Week 18	48	8 (17)	112	52 (46)
Week 22	47	9 (19)	113	55 (49)
Week 26	58	10 (17)	132	68 (52)
1 week follow-up	54	8 (15)	110	46 (42)
2 week follow-up	55	10 (18)	118	26 (22)
4 week follow-up	58	8 (14)	119	24 (20)

1, 2 and 4 week follow-up: indicate follow-ups after study treatment has been halted.

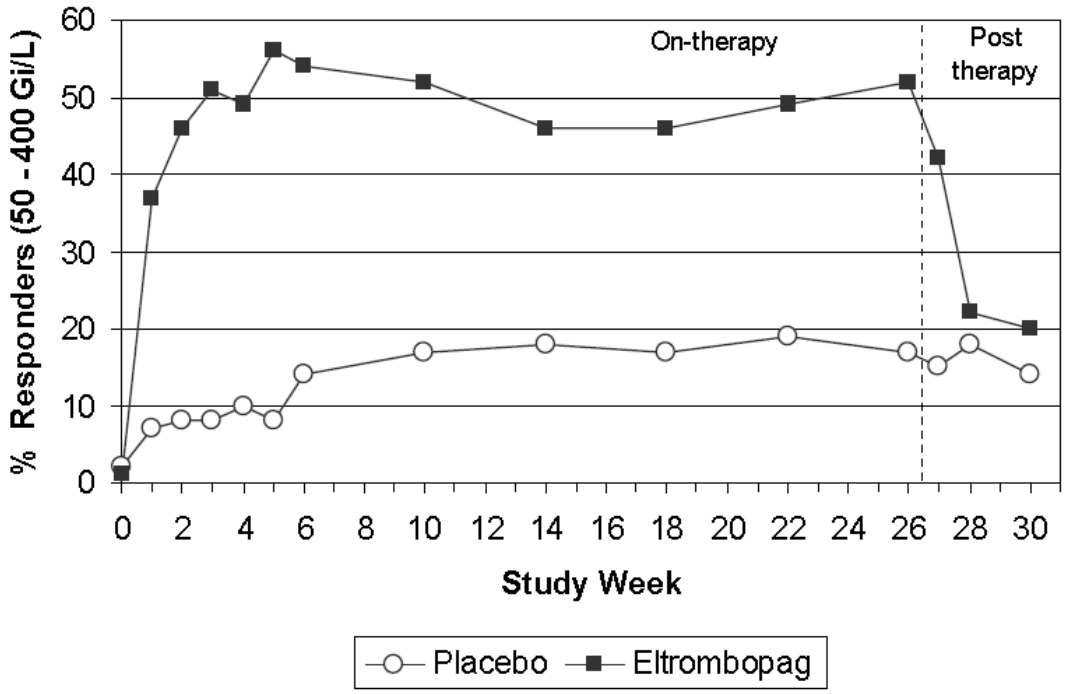


Figure B9 Summary of responders from baseline to follow-up visit in the TRA 102537 RAISE trial (ITT population)

Response was also analysed according to stratification variables. Analysis of the percentage of responders over the entire on-therapy period demonstrated that eltrombopag increased platelet counts irrespective of use of baseline ITP medications (p-value for interaction =0.890), splenectomy status (p-value for interaction = 0.562), or baseline platelet count (p-value for interaction = 0.804) compared to placebo. Response tables for each stratification group are shown in Appendix 2.

Results from secondary efficacy end points

Proportion responding for ≥75% of assessments

The proportion of patients responding for at least 75% assessments was 38% (51 of 134) in the eltrombopag arm compared with 7% (4 of 60) on placebo (OR 10.53, [95% CI 3.48, 31.91]; p<0.0001).

Duration of response

The duration of response was determined using the continuous and cumulative number of weeks of response from all the visits. The mean and median duration of response are presented in Table B21.

Table B21 Duration of platelet response in the TRA 102537 RAISE study, all patients.

	Placebo N=62	Eltrombopag N=135
Continuous duration of response (weeks)		
Evaluable	60[a]	134[a]
Mean (SD)	2.2 (5.5)	9.5 (8.9)
Median (range)	0 (0 – 25[b])	8.1 (0 – 26)
Cumulative duration of response (weeks)		
Evaluable	60	134
Mean (SD)	2.4 (5.9)	11.3 (9.5)
Median (range)	0 (0 – 25)	10.9 (0 – 26)

a. One subject on placebo did not receive study medication and two subjects (one placebo and one eltrombopag) did not have any post-baseline assessments on treatment.

b. There were 8 placebo-treated subjects who responded for ≥40 days. Seven of the 8 subjects did not receive rescue medication prior to their response. One subject received rituximab. One subject (placebo) responded on Day 8 through the remainder of the on-treatment period (177 days).

Post-hoc analysis – "sustained", "transient" and "overall" response

A post hoc analysis of platelet count data was carried out to determine 'sustained', 'transient' and 'overall' platelet responses. Analyses were performed on the intention to treat population and in the subset of patients treated with study medication for 6 months or more.

In both analyses, *sustained response* was defined as having a platelet count elevation ≥50 and ≤400 $X10^9$/L for at least 6 of the last 8 weeks of the treatment period. Patients taking rescue medication at any time were considered to have not achieved a sustained response. Patients who withdrew early were considered not to have achieved a sustained response.

Transient response was defined as platelet count response for ≥4 consecutive weeks during treatment and included all data up to time of withdrawal; platelet count elevations during periods of rescue treatment and up to the time platelet counts fell below 50 $X10^9$/L, were not considered responses.

Overall response was defined as having either a sustained or a transient response, as defined above.

Table B22 Sustained and overall response in the ITT population and for patients treated for over 6 months, by splenectomy status

		Subjects treated for ≥6 months		ITT[a,b,c]	
		Placebo	Eltrombopag	Placebo	Eltrombopag
All Subjects	N	39	95	62	135
	Sustained Response , n (%)	4 (10)	57 (60)	4 (7)	63 (47)
	Overall Response , n (%)	7 (18)	77 (81)	8 (13)	91 (67)
Baseline Splenectomy Status					
Splenectomised	N	12	37	21	50
	Sustained Response , n (%)	1 (8)	19 (51)	1 (5)	20 (40)
	Overall Response , n (%)	2 (17)	26 (70)	2 (10)	30 (60)
Non – splenectomised	N	27	58	41	85
	Sustained Response , n (%)	3 (11)	38 (66)	3 (7)	43 (51)
	Overall Response , n (%)	5 (19)	51 (88)	6 (15)	61 (72)

a. Includes data up to Day 182 for subjects completing 26 weeks (≥182 days) of treatment and data up to last dose of investigational product +3 days for completers with <182 days of treatment.

b. Sustained response: Response (platelets 50-400X109/L, inclusive) for at least 6 of the last 8 wks of treatment. Premature withdrawals and subjects using rescue therapy at any time on treatment are considered as not having sustained response. Subjects with non-weekly assessments are considered to have maintained the same response for each week until their next assessment.

c. Overall response: a sustained or transient response. Transient response: Response for≥4 consecutive weeks during treatment included all data up to time of withdrawal for subjects who prematurely withdrew.

For simplicity the sustained response endpoint in RAISE will be referred to as "durable response" as this endpoint is compared to the durable response endpoint in the romiplostim studies via an indirect treatment comparison.

Median platelet count

Median platelet counts were assessed at each visit. Patients were assessed weekly during the first 6 weeks and at least once every 4 weeks thereafter. Median platelet count for eltrombopag treated patients was maintained between 60 and 80X10^9/L for the majority of visits, whereas the placebo group remained below 30X10^9/L throughout the study (**Error! Reference source not found.**).

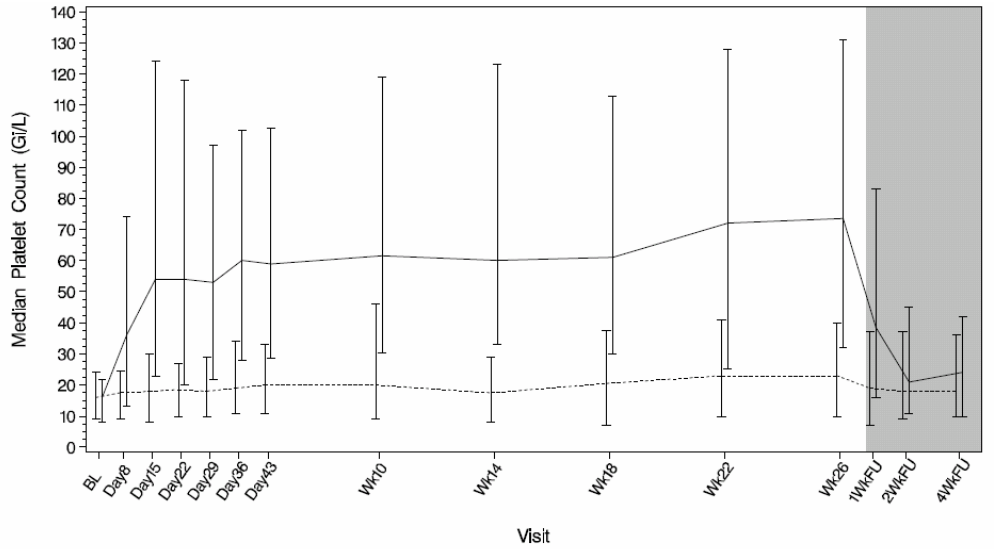


Figure B10 Median platelet count by assessment from baseline to 4 week follow-up in the TRA 102537 RAISE (showing 25th and 75th percentile); solid line: Eltrombopag, dashed line: placebo (ITT)

Risk of bleeding

Bleeding was analysed using three endpoints: at any point throughout the study, at the end of the study, and a post hoc analysis of bleeding at least once at any point during the study[2]. Odds ratios were produced for all bleeding events (WHO grades 1-4), and for clinically significant bleeds (defined as WHO grades 2-4). The tables and graphs generated are shown in Appendix 2.

At baseline, 73% of patients in the eltrombopag group and 77% of patients in the placebo group were experiencing bleeding symptoms (Grade 1-4).

The odds of suffering a bleeding event (Grade 1-4) throughout the 6 month study period were 76% lower in the eltrombopag group than the placebo group (OR: 0.24; p<0.001). At the end of treatment assessment, 57% of patients in the placebo group had bleeding compared with 27% in the eltrombopag group (OR: 0.25, p<0.001). Fewer eltrombopag-treated patients experienced bleeding at least once at any point in the study (79% versus. 93%; OR: 0.21, p=0.012).

At the end of treatment, 13% of the placebo group had clinically significant bleeding (Grades 2-4) compared to 10% of the eltrombopag group. Due to the low incidence of clinically significant bleeding at any one time point, the difference was not statistically significant. However, patients treated with eltrombopag were statistically significantly less likely to have experienced clinically significant bleeding at least once at any point in the study than placebo-treated subjects (33% versus. 53%, OR: 0.30; p=0.002).

A subgroup analysis of bleed rates according to baseline splenectomy status was carried out and is presented in Appendix 2. Eltrombopag-treated patients were statistically significantly less likely to suffer clinically significant bleeding at least once

[2] The analysis of bleeding "throughout the study" used a repeated measures model to analyse the impact of treatment on bleeding at any time point; the analysis of bleeding "at any point during the study" analysed the impact of treatment on the likelihood of patients experiencing one or more bleeds during the study.

at any point during the study, regardless of splenectomy status. Non-splenectomised patients were significantly less likely to have any bleeding if treated with eltrombopag, but for splenectomised patients there was no significant difference between the groups.

Summarisation of the results from the ITP bleeding score were similar to those observed with the WHO bleeding scale and were not reported in Cheng 2011. ITP bleeding score results are therefore not discussed here.

Discontinuation and reduction of concomitant ITP medication

At baseline, 63 patients in the eltrombopag arm (47%) and 31 in the placebo arm (50%) reported use of ITP medications. Of the eltrombopag-treated patients, 37 (59%) reduced or discontinued at least one concomitant ITP medication, compared with 10 (32%) of the placebo group patients (Table B23). The odds of reducing or discontinuing at least one baseline ITP medication were 3 times higher in the eltrombopag-treated group (OR 3.10, p=0.016). Of those who permanently discontinued or had a sustained reduction of at least one ITP medication (31 eltrombopag patients and 6 placebo patients), 77% and 67% respectively discontinued ≥1 baseline ITP medication. While 68% and 50% respectively, discontinued all baseline ITP therapies.

Table B23 Discontinuation and dose reduction of concomitant ITP medication in TRA 102537 RAISE

	Placebo N=62	Eltrombopag N=135
Subjects taking an ITP medication at baseline, n (%)	31 (50)	63 (47)
Reduced/discontinued ≥1 baseline ITP medication, n (%)	10 (32)	37 (59)
OR of reducing/discontinuing ≥1 baseline ITP medication, eltrombopag/placebo [a,b]		3.10
95% CI		1.24, 7.75
p-value (two-sided versus. Placebo)		0.016[c]
Permanently discontinued or had sustained reduction, n (%)	6 (60)	31 (84)
For ≥24 weeks	3 (50)	19 (61)
Permanently discontinued all baseline ITP medication [a,b], n (%)	3 (50)	21[c] (68)
Permanently discontinued ≥1 baseline ITP medication [a,b], n (%)	4 (67)	24[c] (77)

OR: Odds ratio

a. Excludes subjects who subsequently required rescue medication (increase in dose of baseline concomitant medication, new ITP medication, platelet transfusion or splenectomy).

b. Denominators are subjects who either permanently discontinued or had a sustained reduction of baseline ITP medications.

c. Includes one subject (eltrombopag) who was incorrectly identified as receiving a new ITP medication.

Use of rescue medication

Rescue treatment was defined as a composite of: new ITP medication, increased dose of a concomitant ITP medication, platelet transfusion, and/or splenectomy. A total of 40% of the placebo group required rescue medication at some time during the study, compared to only 18% in the eltrombopag group. The odds ratio for use of rescue medication in the eltrombopag compared with the placebo group was 0.33 (95% CI 0.16, 0.64; p=0.001). A breakdown of rescue medication use is given in Appendix 2.

Haemostatic challenge

Fourteen eltrombopag-treated patients (10%) and 4 placebo-treated patients (7%) experienced haemostatic challenges on study. Two of the placebo patients required rescue therapy after dental procedures. In the eltrombopag group, 4 of the 14 patients received additional ITP therapy; 3 of these had not consistently responded to eltrombopag and had platelet counts below $40x10^9$/L at the time of the challenge. The remaining eltrombopag-treated patient who received additional ITP therapy had platelet counts of $123x10^9$/L and received a platelet transfusion during surgery for an abdominal aortic aneurysm.

Health related quality of life (HRQoL)

HRQoL was assessed at baseline and weeks 6, 14 and 26 or at study withdrawal. Patients in the eltrombopag group had greater improvements from baseline to week 26 across the majority of health and well-being domains of the SF-36 instrument compared to those in the placebo group. Differences between treatments in mean change from baseline were statistically significant for physical role (5.4 [95% CI 0.5 to 10.3]; p=0.030), vitality (3.9 [95% CI 0.1 to 7.7]; p=0.045), emotional role (5.4 [95% CI 0.8 to 10.1]; p=0.023) and the mental health component summary (2.1 [95% CI 0.2 to 4.0]; p=0.030). Eltrombopag treatment resulted in statistically non-significant improvements in three additional domains compared with placebo: physical function (2.8 [95% CI -1.1 to 6.7]; p=0.154), general health (2.4 [95% CI -1.6 to 6.5]; p=0.243), and mental health (2.5 [95% CI - 0.9 to 6.0]; p=0.154).

Exposure to study medication

Exposure to eltrombopag and placebo is summarised in Table B24.

Table B24 Exposure to study medication in the TRA 102537 RAISE study

	Placebo N=61	Eltrombopag N=135
Average Daily Dose, mg		
N	61	134
Mean daily dose (SD)	68.40 (8.82)	55.20 (16.26)
Median (min-max)	71.90 (31-73)	58.00 (16-72)
Cumulative dose over whole study period, mg		
N	61	134
Mean (SD)	11775.00 (3428.64)	9178.90 (3833.24)
Median (min-max)	13025 (350-15825)	9450 (250-14550)
Days on Study Drug		
N	61	134
Mean (SD)	169.30 (43.16)	164.70 (45.09)
Median (min-max)	183 (7-218)	183 (5-201)

Dose modification

The starting dose for all patients was 50mg/day. Dose modifications were allowed to achieve and maintain a platelet count of 50-400 $x10^9$/L. The mean daily dose of eltrombopag levelled out at approximately six weeks at just over 50mg per day and remained stable for the remainder of the study (graph shown in Appendix 2).

Of patients treated with eltrombopag, 94 (70%) had an increase and 54 (40%) had a decrease in dose and/or frequency of administration at some time during the treatment period. Of those with dose increases, 75 of 94 (80%) increased their eltrombopag dose from 50mg to 75 mg at least once. Seventeen of 94 (18%) initially decreased from 50 mg to 25 mg, followed by an increase back to 50mg. One patient decreased their dose to <25mg (reducing the frequency of administration), before reverting to 25mg.

5.6 Meta-analysis of eltrombopag studies

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

A systematic review was conducted to obtain all the relevant evidence relating to the clinical and cost effectiveness of eltrombopag and relevant comparators in the treatment of immune thrombocytopenia (ITP). The inclusion criteria and search strategy used are described in Section 5.1 and Appendix 2.

Of the RCTs identified from the systematic review, only three evaluated eltrombopag (TRA100773A[40]; TRA100773B[42], and TRA102537 RAISE[38;39]).

The consistency and comparability of reported efficacy outcomes between identified studies and availability of actual data were considered, to ensure that only comparable studies were combined in any meta-analysis.

The three studies (TRA100773A[40]; TRA100773B[42]; TRA 102537 RAISE[38;39]) were considered eligible for the meta-analyses. Data were combined using standard methods (Mantel-Haenszel fixed and random effects method) and expressed as Odds Ratios with 95% confidence intervals. The I^2 statistic was also calculated to describe the proportion of variability in effect estimates due to heterogeneity rather than chance.

Data were available for a single outcome: platelet count ≥ $50x10^9$/L at day 43.

Treatment with eltrombopag was associated with a significantly higher chance of achieving the primary outcome (a platelet count of > $50x10^9$/L at 6 weeks of treatment) compared with placebo (OR (fixed effect) [95% CI] = 8.23 [4.68, 14.48] (Figure B11); OR (random effect) [95% CI] = 8.16 [4.63, 14.37] (Figure B12).

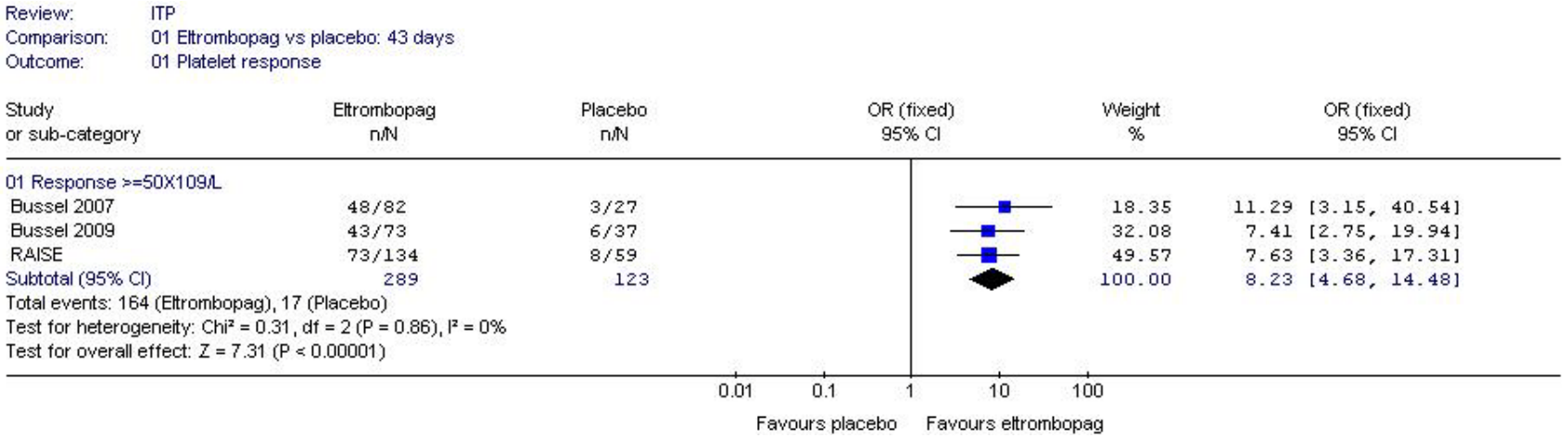


Figure B11 Eltrombopag versus placebo: forest plot of achieving platelet count ≥ 50 X10^{9}/L using fixed-effect Odds Ratio

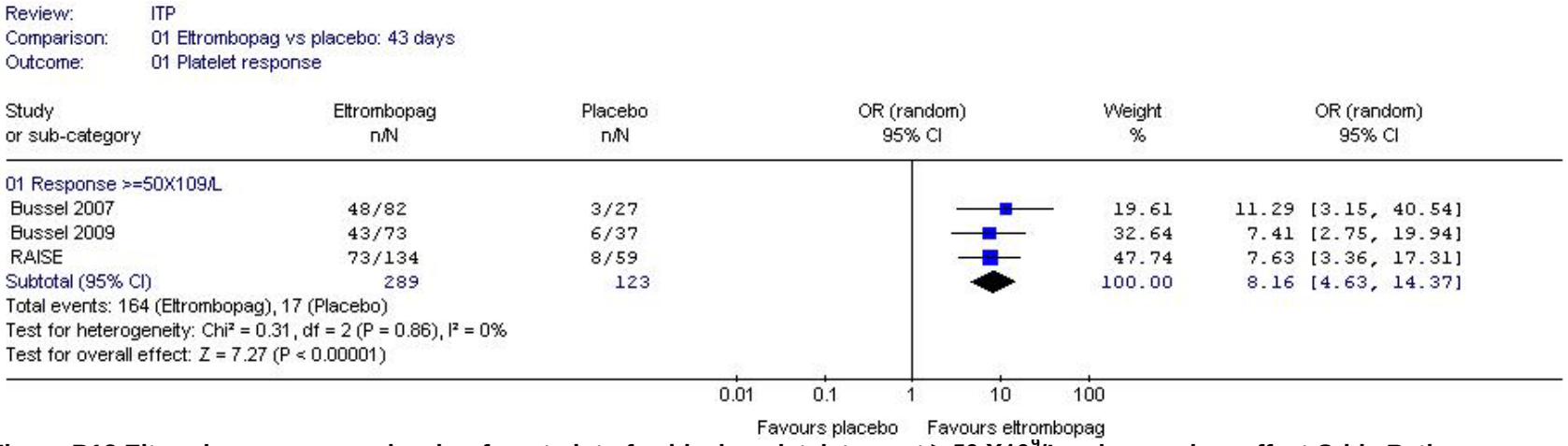


Figure B12 Eltrombopag versus placebo: forest plot of achieving platelet count ≥ 50 X10^{9}/L using random-effect Odds Ratio

5.7 Indirect and mixed treatment comparisons

Data from head-to-head RCTs should be presented in the reference-case analysis, if available. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

There are no head to head data comparing eltrombopag with romiplostim or other active treatments. Indirect treatment comparison methods were therefore considered in order to evaluate the relative efficacy of treatments specified in the decision problem.

Romiplostim indirect comparison

5.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in Appendix 4.

In addition to recommending eltrombopag for the second-line treatment of ITP the International Consensus Report (ICR) for ITP[7] recommends another TPO-RA: romiplostim. Romiplostim is licensed for the same chronic, relapsed/refractory ITP patient group as eltrombopag and has received approval from NICE for the treatment of adults with cITP whose condition is refractory to standard active treatments and rescue therapies, or who have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies (in conjunction with a patient access scheme)[33]. Rather than preferentially recommending either eltrombopag or romiplostim, the International Consensus Report provides a general recommendation for the use of TPO-RAs for the treatment of ITP[7].

Romiplostim studies were identified by the systematic review; the search strategies are documented in Section 5.1 and Appendix 2.

5.7.2 Please follow the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 9.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Identified studies are presented in Table B25 and Table B26. Reasons for inclusion or exclusion from further discussion are provided. Two of the identified RCTs, both reported in a single paper (Kuter 2008[60]), are included. Two non-RCTs are also included[61;62].

Two non-RCTs studies already included in the eltrombopag section, also included patients receiving romiplostim (Meyer 2011[50] and Kuter ASH 2011[51]). These studies are therefore discussed in section 5.9.

Table B25 List of identified romiplostim RCTs

Trial no.	Intervention	Comparator	Population	Justification for inclusion/exclusion
Bussel 2006[63]	Romiplostim dose finding (1 µg/kg (n=8), 3 µg/kg (n=8), 6 µg/kg (n=1) or placebo (n=4) per week for 6 weeks)	placebo	N = 21, Aged 18 – 65 years Platelet count < 30X109/L for patients not receiving corticosteroids and < 50X109/L for those receiving corticosteroids	Identified as part of the systematic review, however excluded as small dose finding study
Kuter 2008[60;64;65]	Romiplostim 1µg/kg starting dose (up to 15 µg/kg)	placebo	Splenectomised N=63 All participants ≥18 years, platelet count <30X109/L ≥ 1 prior ITP treatments	Evaluation of the safety and efficacy of romiplostim in a splenectomised population; study included
Kuter 2008[60;64;65]	Romiplostim 1µg/kg starting dose (up to15 µg/kg)	placebo	Non-splenectomised N=62 All participants ≥18 years, platelet count <30X109/L ≥ 1 prior ITP treatments	Evaluation of the safety and efficacy of romiplostim in a non-splenectomised population; study included
Kuter 2010[66]	Romiplostim 3µg/kg starting dose (up to10 µg/kg)	medical standard of care	N = 234 Non-splenectomised, ≥1 prior ITP medication, platelet count of <50 X109/L	Excluded for the following reasons: • platelet count for inclusion in the study was <50X109/L • median platelet counts was 29X109/L (range: 1-123) • 36% patients had persistent, not chronic ITP
Shirasugi 2011[67]	Romiplostim 3µg/kg starting dose (up to10 µg/kg)	placebo	ITP diagnosis of ≥6 months, ≥1 prior ITP medication, platelet count of ≤30X109/L, ≥20 years, Japanese race	Evaluation of the safety and efficacy of a Japanese population. Relevance to UK decision problem limited; study excluded.

Table B26 List of identified romiplostim non-RCTs

Trial no.	Intervention	Population	Justification for inclusion/exclusion
Newland, 2006[68]	Romiplostim 30µg (n=4),100µg (n=4), 300 µg (n=7) and 500µg (n=1) Two administrations of the assigned dose (subcutaneous injection) on day 1 and on day 15 or 22	N=16, ITP diagnosis; two of three platelet counts taken during the screening had to be <30X10^9/l in patients not receiving ITP treatment	Identified as part of the systematic review, however it is a dose finding study and does not reflect the licenced regimen; study excluded.
Bussel 2009, Bussel ASH 2009, Kuter ASH 2010[61;64;69]	Romiplostim, doses were adjusted to achieve the target platelet count of 50X10^9/L to 200 X10^9/L (see Appendix 4 for algorithm)	Participants of a previous romiplostim study, whether they had received romiplostim or placebo.	Long term extension study evaluating the safety and efficacy of romiplostim from previous studies: Bussel 2006, Kuter 2008 and Newland 2006; study included
Shirasugi 2009[70]	Romiplostim (1, 3, or 6µg/kg)	Japanese patients aged 20-70, diagnosis of ITP >6months, baseline platelet count <30X10^9/L, had ≥1 prior ITP medication	Safety and efficacy in a Japanese population, relevance to UK decision problem limited; study excluded.
Janssens ASH 2011 and EHA 2011[62;71]	Romiplostim (1µg/kg starting dose)	≥18 years, ≥ 1 prior ITP medication, baseline platelet count of <30X10^9/L (final amendment).	Evaluates the safety and efficacy of romiplostim in adults with primary ITP; study included
Khellaf 2011[72]	Romiplostim 1µg/kg starting dose (up to 10µg/kg)	N=72, ITP according to ASH guidelines Failure of successive treatments with corticosteroids and/or IVIg	Although median platelet count at baseline was 11x10^9/L, patients could be included with counts >30X10^9/L. Baseline range was 1-60X10^9/L therefore paper was excluded.

5.7.3 Relevant romiplostim RCTs

5.7.4 Kuter 2008[60;64;65]: summary of trials

Methodology, design and inclusion criteria

Details of methodology and study designs for these trials are shown in Table B27. Inclusion criteria are shown in Table B28.

Kuter 2008 reports the pooled analysis of two identical trials, one in splenectomised and one in non-splenectomised patients. The primary outcome was durable platelet response, defined as six or more weekly responses in the last eight weeks of treatment with no use of rescue therapy at any point during the trial. Reductions in concomitant ITP therapy were allowed in the first 12 weeks but was not allowed during the last 12 weeks of the study.

A critical appraisal of the trial is given in Appendix 5. The critical appraisal found the study was, in general, methodologically strong. The FDA did however note some imbalances between the study arms of the trials which should be considered when interpreting the results (see Section 5.11 for further discussion)[65].

Table B27 Methodology of Kuter 2008 trials

Location	International (USA and Europe including France, the Netherlands, Spain and the UK, 35 sites)
Design	Two pooled phase III, randomised, double-blinded, placebo controlled trials
Duration of studies	Treatment phase was 6 months.
Method of randomisation	Subjects were recruited into two trials; those who had received splenectomy, and those who had not. Within each trial patients were subsequently randomised 2:1, romiplostim to placebo. A randomisation sequence was generated in house by Amgen Inc. using the block randomisation method. Patients were stratified according to use of baseline concurrent ITP medication.
Method of blinding (care provider, patient and outcome assessor)	Patients and physicians were both blinded, it is unclear whether outcome assessors were blinded. Treatments were allocated using an interactive voice recognition system (IVRS) and romiplostim and placebo were provided in identical vials to maintain blinding
Intervention	Romiplostim (n=42 splenectomised, n=41 non-splenectomised) The dose of study medication was adjusted based on individual platelet counts. Starting dose was 1µg/kg administered intravenously once a week. To achieve the target platelet count of $50X10^9$/L to $200X10^9$/L, doses were adjusted by: 2 µg/kg every week if the count was $10X10^9$/L or less and 2µg/kg every 2 weeks if $11X10^9$/L to $50X10^9$/L. Once platelets reached more than 50 $X10^9$/L, the maintenance algorithm was used: dose was increased by 1 µg/kg every week if $10X10^9$/L or less; increased by 1 µg/kg after 2 weeks if $11X10^9$/L to $50X10^9$/L; reduced by 1 µg/kg after 2 consecutive weeks at $201X10^9$/L to $400X10^9$/L; withheld if more than $400X10^9$/L and subsequent doses reduced by 1 µg/kg and given after count was less than $200X10^9$/L. The maximum allowed dose was 15µg/kg. If platelet counts were >$100X10^9$/L within the first 12 weeks then reduction in concomitant ITP therapy was permitted. Reductions in concomitant therapy were not allowed in the last 12 weeks.
Comparator	Placebo (n=21 splenectomised, n=21 non-splenectomised)
Primary outcomes	Durable platelet response, defined as weekly platelet responses (≥$50X10^9$/L) during 6 or more weeks of the last 8 weeks of treatment. Patients who received rescue medication at any point during the study could not be counted as having a durable response.
Secondary outcomes	• Transient platelet response was defined as ≥4 weekly responses without a durable response from weeks 2-25. Observations occurring in the eight-weeks following receipt of rescue medication (see definition below) were not counted as responses • Frequency of overall response (durable + transient response) • Number of weekly platelet responses • Proportion of patients needing rescue medication (defined as an increased dose of concomitant ITP therapy, or the use of any new drug to increase platelet counts) • The frequency of durable platelet response with a stable dose (dose maintained within 1µg/kg in last 8 weeks) • Changes in concurrent ITP medications • Health related quality of life (EQ-5D, ITP-PAQ) • Adverse events
Duration of follow-up	Observed for 12 weeks after discontinuation of study.

Table B28 Inclusion criteria of Kuter 2008 trials

Inclusion Criteria	Two parallel studies were carried out enrolling patients who were: 1) Splenectomised 2) Non-Splenectomised All other inclusion criteria were the same: • Aged ≥18 years • Diagnosis of ITP according to American Society of Hematology (ASH) guidelines • At least 1 previous treatment for ITP • Pre-treatment platelet count < $30X10^9$/L (mean of 3 counts during screening) • No pre-treatment individual platelet count > $35X10^9$/L • Haemoglobin of at least 9.0 g/dL at baseline • Over 60 years of age: Chronic ITP documented by bone marrow to exclude myelodysplastic syndrome (MDS)
Exclusion Criteria	• Other ITP therapies had to last be administered at least 14 weeks prior to enrolment for rituximab, 8 weeks for alkylating agents, 2 weeks for IVIg or Anti-D and 4 weeks for any other therapies. • Splenectomy had to have been undertaken ≥4 weeks previously

Baseline characteristics

The baseline characteristics of the participants in Kuter 2008 are provided in Table B29.

A total of 125 participants were included, 83 in the romiplostim arm and 42 in the placebo arm (splenectomised patients: 21 placebo, 42 romiplostim, non-splenectomised: 21 placebo, 41 romiplostim). Median age was 52 and women accounted for 65% of the population. The trial population was largely Caucasian (82%). Splenectomised patients had been diagnosed with ITP for a median of 7.75 and 8.50 years in the romiplostim and placebo arms. Non-splenectomised patients had been diagnosed with ITP for a median of 2.20 and 1.60 years. Patients had a baseline platelet count of $16x10^9$/L, and 63% had received three or more prior ITP medications (see Appendix 4 for further details of prior treatment). Nearly a third of patients (31%) were receiving concomitant ITP medication at baseline.

Table B29 Baseline characteristics of participants in Kuter 2008 trials

	Splenectomised Patients		Non-Splenectomised Patients		All Patients from both studies		
	Placebo (n=21)	Romiplostim (n=42)	Placebo (n=21)	Romiplostim (n=41)	Placebo (n=42)	Romiplostim (n=83)	Total (n=125)
Age (years)	56 (26-72)	51 (27-88)	46 (23-88)	52 (21-80)	52 (23-88)	52 (21-88)	52 (21-88)
Women, n (%)	11 (52)	27 (64)	16 (76)	27 (66)	27 (64)	54 (65)	81 (65)
Race, n (%)							
White	19 (91)	34 (81)	18 (86)	31 (76)	37 (88)	65 (78)	102 (82)
Black/African American	2 (10)	3 (7)	1 (5)	3 (7)	3 (7)	6 (7)	9 (7)
Hispanic/Latino	0	3 (7)	2 (10)	3 (7)	2(5)	6 (7)	8 (6)
Other*	0	2 (5)	0	4 (10)	0	6 (7)	6 (5)
Weight (kg)	89 (57-169)	77 (45-138)	71 (52-123)	78 (44-134)	81 (52-169)	78 (44-138)	79 (44-169)
Median duration of ITP (years since diagnosis)	8.50 (1.1-31.4)	7.75 (0.6-44.8)	1.60 (0.1-16.2)	2.20 (0.1-31.6)	NR	NR	NR
≥3 previous treatments, n (%)	20 (95)	39 (93)	5 (24)	15 (37)	26 (60)	54 (65)	79 (63)
Platelet count† ($X10^9$/L)	15 (2-28)	14 (3-29)	19 (5-31)	19 (2-29)	18 (2-31)	16 (2-29)	16 (2-31)
Thrombopoietin concentration (pg/mL) ‡	124 (31-774)	113 (31-586)	81 (31-1848)	94 (31-1228)	108 (31-1848)	102 (31-1228)	103 (31-1848)
Receiving concomitant ITP therapy, n (%)	6 (29)	12 (29)	10 (48)	11 (27)	16 (38)	23 (28)	39 (31)

data are median (minimum-maximum) or number (%). ITP: immune thrombocytopenia, *Includes Asian and native Hawaiian or other Pacific Islanders, †Baseline platelet count=mean of platelet count at days -8, -2 and pre-dose day 1, ‡Normal thrombopoietin concentration ranges from 32-246pg/mL

Results

Primary end point : durable platelet response

The primary outcome was durable platelet response, defined as weekly platelet responses during six or more weeks of the last eight weeks of treatment. Patients who received rescue medications at any time during the study could not be counted as having a durable response. Durable response results are shown in Table B30.

In splenectomised patients the odds of achieving a durable response were 26.77 times higher in the romiplostim arm versus placebo (95% CI 1.52, 472.41) (Table B30). In non-splenectomised patients the odds ratio of achieving a durable response was 31.25 favouring romiplostim versus placebo (95% CI 3.81, 256.24).

Secondary endpoint:

Further analyses showed the proportion of patients achieving a durable platelet response whilst maintaining a stable dose (±1µg/kg in the last eight weeks of the study), and proportion achieving durable response regardless of use of rescue therapy.

Overall platelet response

The secondary response outcome was overall response, defined as durable plus transient rates of platelet response. Transient response was defined as four or more weekly platelet responses without a durable response from week 2 to 25. The OR for overall response in splenectomised patients was 151.63 for romiplostim compared to placebo (95% CI 8.39, 2741.84) (Table B30). The OR in non-splenectomised patients was 43.20 (95% CI 9.27, 201.33).

The wide confidence intervals around the two treatment effects are the result of small sample sizes.

Table B30 Platelet response results for romiplostim[60;73-75]

Endpoint	Splenectomised patients			Non-splenectomised patients			All patients		
	Placebo (n=21)	Romiplostim (n=42)	p-value	Placebo (n=21)	Romiplostim (n=41)	p-value	Placebo (n=42)	Romiplostim (n=83)	p-value
Durable Platelet response									
OR versus. placebo		26.77	NR		31.25	NR		40.02	
95% CI		1.52, 472.41	NR		3.81, 256.24	NR		5.26, 304.70	
Incidence Rate, n (%)	0	16 (38.1)	0	1 (4.8)	25 (61.0)	<0.0001	1 (2.4)	41 (49.4)	<0.0001
95% CI	0.0, 16.1	23.6, 54.4	NR	0.1, 23.8	44.5-75.8	NR	0.1, 12.6	38.2, 60.6	NR
Overall platelet response									
OR versus. placebo		151.63	NR		43.20	NR		64.07	
95% CI		8.39, 2741.84	NR		9.27, 201.33	NR		17.33, 236.82	
Incidence Rate, n (%)	0	33 (78.6)	<0.01	3 (14.3)	36 (87.8)	<0.0001	3 (7.1)	69 (83.1)	<0.0001
95% CI	0.0, 16.1	63.2, 89.7	0.0, 16.1	3.0, 36.3	73.8-95.9	NR	1.5, 19.5	73.3, 90.5	NR
No. weeks with platelet response									
Mean	0.2	12.3	0.2	1.3	15.2	<0.0001	0.8	13.8	<0.0001
SD	0.5	7.9	0.5	3.5	7.5		2.5	7.8	NR
Durable platelet response with stable dose									
Incidence, n, (%)	0	13 (31)	0	0	21 (51.2)	<0.0001	0	34 (41.0)	<0.0001
95% CI	0.0, 16.1	17.6, 47.1	0.0, 16.1	0.0, 16.1	35.1, 67.1		0.0, 8.4	30.3, 52.3	
Durable platelet response regardless of rescue therapy use									
Incidence, n, (%)	1 (5)	19 (45)	NR	3 (14)	27 (66)	NR	4 (10)	46 (55)	NR

OR: odds ratio, CI: confidence interval; SD: standard deviation

Incidence and severity of bleeding

Bleeding events were captured as adverse events, graded as 1=mild, 2=moderate, 3=severe, 4=life-threatening, 5=fatal (no standard scale was reportedly used).

The odds of suffering a Grade 2 or greater bleeding event are shown in Table B31. Overall, the odds of suffering a moderate or worse (Grade ≥2) bleeding event were 65% lower (OR= 0.35, 95% CI: 0.14, 0.85) in patients treated with romiplostim compared to placebo.

Table B31 Grade 2 (moderate) or greater bleeding events in Kuter 2008

	Splenectomised		Non-splenectomised		All	
	Placebo N=21	Romiplostim N=42	Placebo N=20	Romiplostim N=42	Placebo N=41	Romiplostim N=84
Incidence Grade ≥2, n (%)	8 (38.1)	9 (21.4)	6 (30.0)	4 (9.5)	14 (34.1)	13 (15.5)
OR (romiplostim versus. placebo)		0.44		0.25		0.35*
95% CI		0.14, 1.40		0.06, 1.00		0.14, 0.85

OR: odds ratio, CI: confidence interval

*p=0.018, post hoc analysis comparing bleeding event between total placebo and romiplostim

The OR for a clinically significant bleed (Grade ≥3) was 0.55 (95% CI: 0.16, 1.96) with romiplostim compared to placebo; the odds reduction did not reach statistical significance (Table B32).

Table B32 Grade 3 or greater (clinically significant) bleeding events in Kuter 2008

	Splenectomised		Non-Splenectomised		All	
	Placebo N=21	Romiplostim N=42	Placebo N=20	Romiplostim N=42	Placebo N=41	Romiplostim N=84
Incidence ≥ Grade 3, n (%)	4 (19.0)	4 (9.5)	1 (5.0)	2 (4.8)	5 (12.2)	6 (7.1)
OR (romiplostim versus. placebo)		0.45		0.95		0.55
95% CI		0.10, 2.00		0.08, 11.14		0.16, 1.96

OR: odds ratio; CI: confidence interval

Dose modification or discontinuation of concurrent ITP medication

31% of all patients included in Kuter 2008 were receiving concurrent ITP medication at baseline. Dose decrease or discontinuation of concurrent ITP medications was allowed only during the first 12 weeks if platelet counts were more than 100 $x10^9$/L. No decrease or discontinuation was allowed thereafter; increases were allowed at any time. Participants who were able to discontinue concomitant medications after the treatment period were also noted. Details are shown in Table B33.

Table B33 Discontinuation of concomitant ITP medication in Kuter 2008

	Splenectomised		Non-Splenectomised	
	Placebo	Romiplostim	Placebo	Romiplostim
Receiving concomitant ITP medication at baseline, n	6	12	10	11
Discontinued at 25 weeks, n (%)	0/6 (0)	8/12 (67)	3/10 (30)	4/11 (36)

Exposure to study medication

In the first 12 weeks of the study the mean dose of romiplostim was 3-4µg/kg, compared to over 10µg/kg in the placebo arm. The overall median dose of romiplostim was higher in the splenectomised group at approximately 3µg/kg, compared to 2µg/kg in the non-splenectomised group.

A graph showing mean study dose published in Kuter 2008 shows a gradual increase in romiplostim dose over the first ~3 weeks in splenectomised and non-splenectomised patients. The increase plateaus thereafter although the mean dose continues to vary throughout the treatment period (week 24).

Requirement for rescue medication

In both splenectomised and non-splenectomised patients, treatment with romiplostim reduced the need for rescue medication (Table B34). Details of rescue medication use are given in Appendix 4.

Table B34 Rescue medication requirement in Kuter 2008

	Splenectomised		Non-Splenectomised		All	
	Placebo N=21	Romiplostim N=42	Placebo N=20	Romiplostim N=42	Placebo N=41	Romiplostim N=84
Incidence, n (%)	12 (57.1)	11 (26.2)	13 (61.9)	7 (17.1)	25 (59.5)	18 (21.7)

5.7.5 **Indirect comparison of eltrombopag and romiplostim: methodology**

5.7.6 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

A network diagram of the studies included in the indirect comparison of eltrombopag and romiplostim is shown in Figure B13.

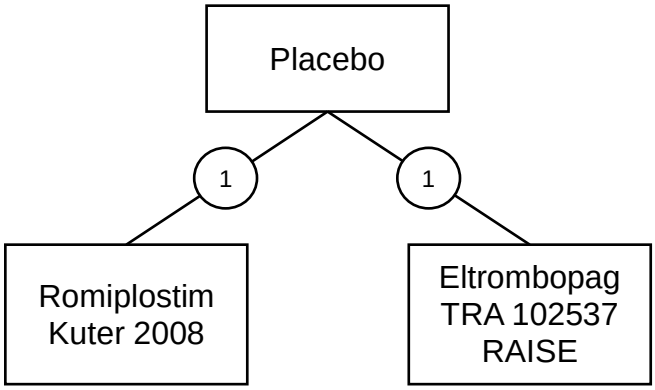


Figure B13 Number of studies included in the indirect comparison of eltrombopag (n=1) and romiplostim (n=1)

Study populations

The inclusion criteria stated in RAISE and Kuter 2008[60;64;65] indicate that the studies were designed to recruit a similar, chronic, refractory ITP population (see Table B11 and Table B29). Where possible the 95% confidence intervals around the baseline characteristics of each trial were calculated (Figure B14) or a summary was provided (Table B35). Baseline characteristics were seen to overlap in the overall patient populations. Differences are likely to be attributable to the heterogeneous nature of the patient population, the diversity of countries where trials were conducted and the relatively small number of patients in each trial.

The most notable differences were in the duration of ITP, the proportion of patients who had received three or more prior ITP medications and the proportion of patients receiving concomitant medication. These and other minor differences in the baseline characteristics are primarily driven by the proportion of splenectomised patients in each study. RAISE allowed recruitment of splenectomised and non-splenectomised patients. The Kuter 2008 study, however, reported the pooled results of two parallel trials; one which recruited only splenectomised patients and one which recruited only non-splenectomised patients[60;64;65]. This led to proportionally more splenectomised patients in Kuter 2008[60;64;65] compared to RAISE (50% versus 36%). Of note, the RAISE study had numerically more splenectomised patients than the Kuter study.

Splenectomised patients represent a more heavily pre-treated population than non-splenectomised patients (Figure B12). Overall, Kuter 2008 trial had a slightly greater proportion of patients who had received three or more prior treatments compared to

RAISE, (63% versus 54%), although confidence intervals are overlapping (Figure B15). Once stratified by splenectomy status the differences between the studies are reduced (≥3 prior therapies: 32% for Kuter 2008[60;64;65] versus 36% for RAISE in the non-splenectomised patients, 94% versus 86% in the splenectomised patients).

Kuter 2008 presented patients who had been diagnosed with ITP for appreciably longer than in RAISE (see Table B35). However, when splenectomy status is taken into account this difference becomes less pronounced.

There was a marked difference in the types of prior ITP medication used between Kuter 2008 and RAISE (Figure B15), with greater use of IVIg, Anti-D, rituximab and cyclophosphamide in Kuter 2008. This is reflective of the diversity of countries where the trials were conducted, where standard of care and availability of different medications varies. These are likely to account for the differences seen in the trials.

The time since diagnosis and multiple number of prior ITP treatments in both trials indicate the chronic and highly refractory nature of the populations enrolled.

There was a higher rate of baseline concomitant medication use in RAISE (47% in the eltrombopag and 50% in the placebo arms) compared to Kuter 2008 (28% in the romiplostim and 38% in the placebo arms).

These types of imbalances are more likely within small trials, conducted in different countries and in heterogeneous patient populations. On the basis of an assessment of the pivotal studies and the fact that the drugs are licensed to treat the same patient population, we determined that it was appropriate to conduct an indirect treatment comparison. This is not withstanding the uncertainty associated with such analyses, which is increased in this case by the heterogeneity in patients being compared and the differences in study design between the trials (described below). The results of the indirect comparison should be interpreted with caution.

Table B35 Baseline ITP duration and platelet count in RAISE and Kuter 2008, by splenectomy status

	Splenectomised		Non-Splenectomised		All	
TRA 102537 RAISE	Eltrombopag n=50	Placebo n=21	Eltrombopag n=85	Placebo n=41	Eltrombopag n=135	Placebo n=41
Median ITP duration (year)	4.37 (0.17-23.42)	5.23 (0.42-36.42)	1.03 (0.08-19.66)	1.79 (0.16-17.00)	NR	NR
Median platelet count ($X10^9$/L)	13.5 (1.0-30.0)	12.0 (3.0-87.0)	16.0 (0.0-78.0)	18.0 (2.0-28.0)	16.0 (8.0-22.0)	16.0 (9.0-24.0)
Kuter 2008	Romiplostim n=42	Placebo n=21	Romiplostim n=41	Placebo n=21	Romiplostim n=83	Placebo n=42
Median ITP duration (year)	7.75 (0.60-44.80)	8.50 (1.10-31.40)	2.20 (0.10-31.60)	1.60 (0.10-16.20)	NR	NR
Median platelet count ($X10^9$/L)	14.0 (3.0-29.0)	15.0 (2.0-28.0)	19.0 (2.0-29.0)	19.0 (5.0-31.0)	16.0 (2.0-29.0)	18.0 (2.0-31.0)

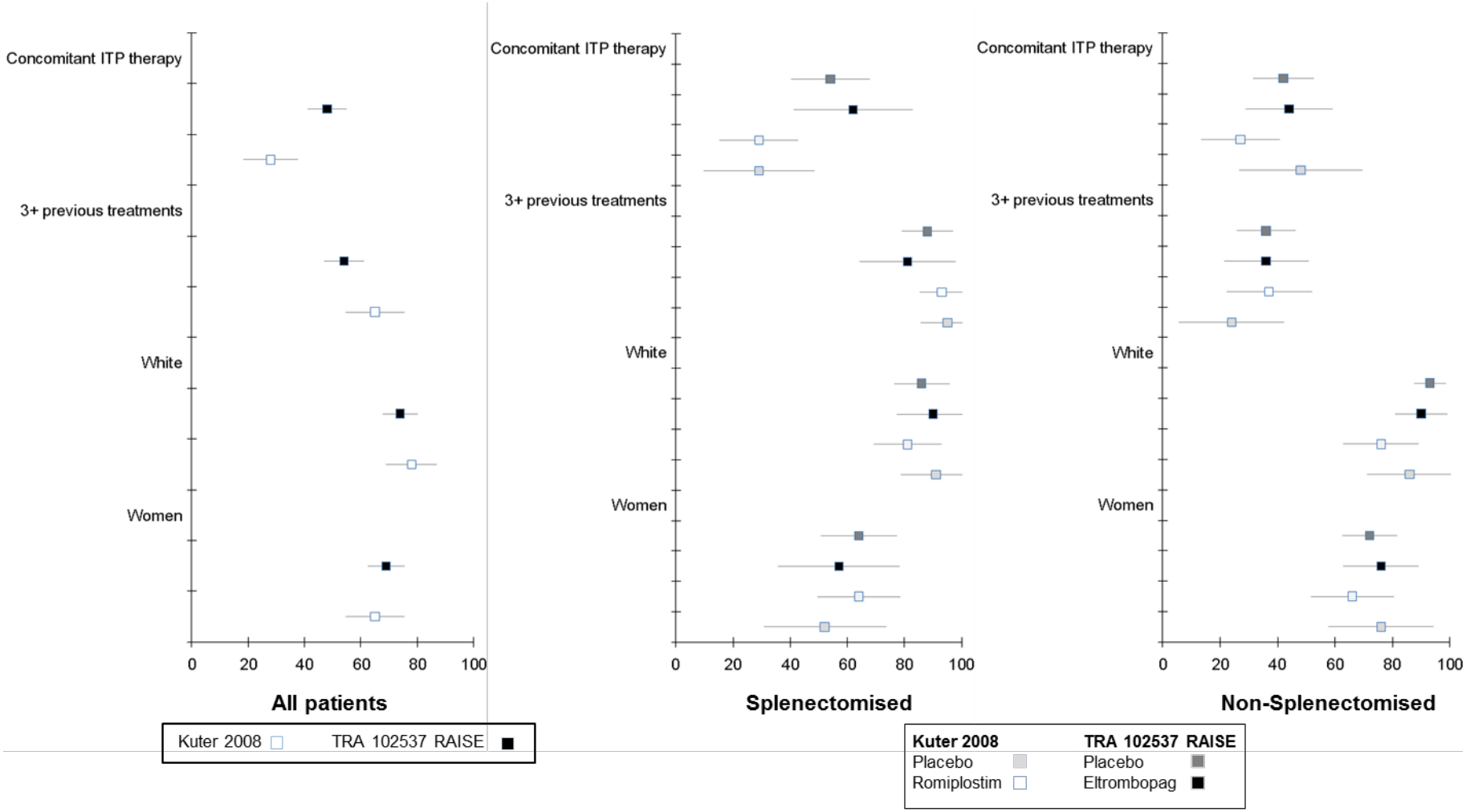


Figure B14 95% confidence intervals of the baseline characteristics of TRA 102537 RAISE and Kuter 2008 for all patients and by splenectomy status

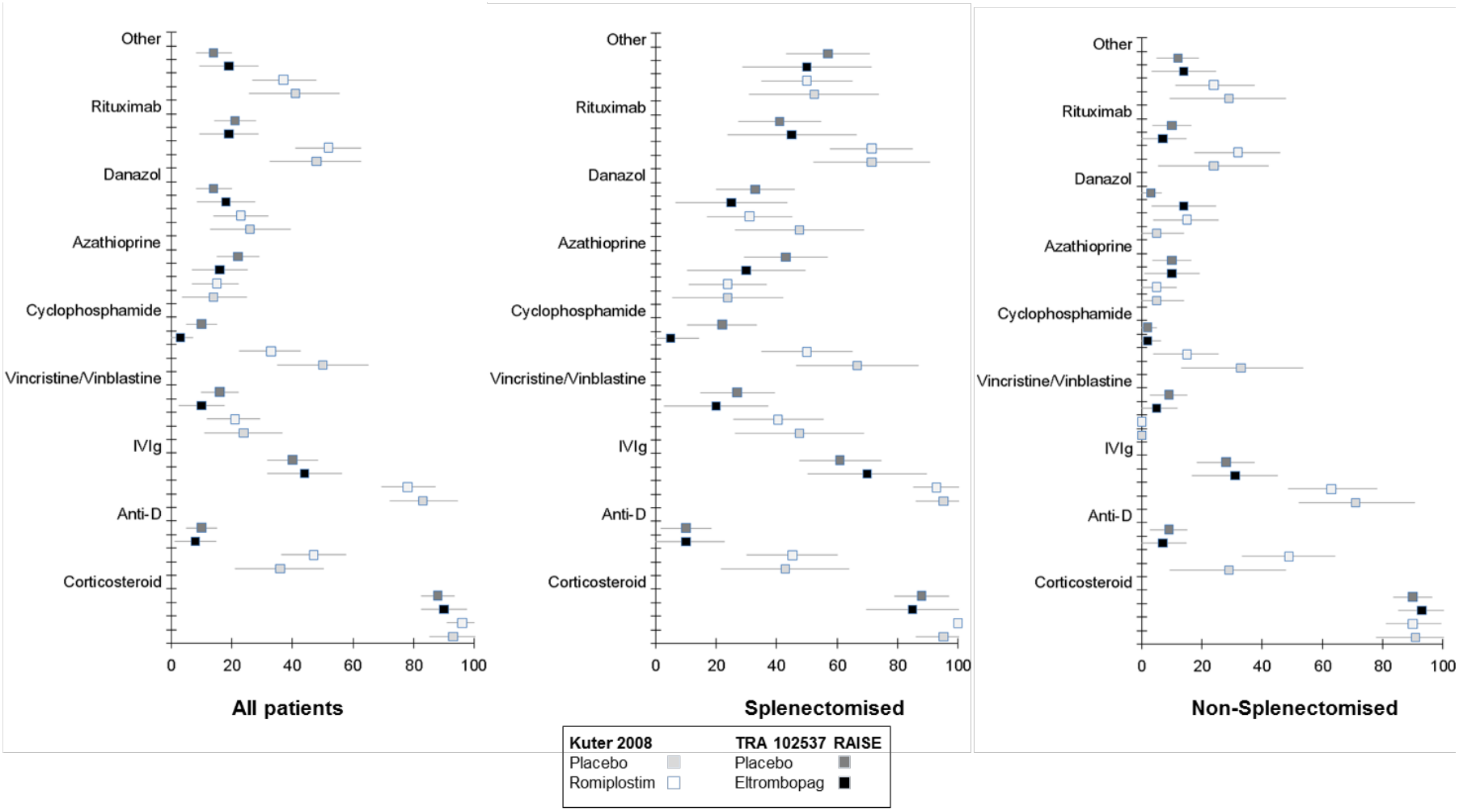


Figure B15 95% confidence intervals for prior ITP medications received by participants in placebo and treatment arms in TRA 102537 RAISE and Kuter 2008 for all patients, and by splenectomy status.

5.7.7 For the selected trials, provide a summary of the data used in the analysis.

Indirect comparisons were carried out on the following endpoints:

- Platelet response endpoints:
  - Overall response
  - Durable response
- Bleeding event endpoints:
  - Moderate or worse bleeding events (CTCAE grade ≥2)
  - Clinically significant bleeding events (CTCAE grade ≥3)

The definitions and data sources used to facilitate each indirect comparison are provided below.

Platelet response definitions

The platelet response endpoints differed between the trials. The primary outcome in RAISE was the odds of response (platelet count of 50 to 400x10^9/L) to eltrombopag versus placebo at any point during the 6 month treatment period. Patients who received rescue treatments were regarded as non-responders for the duration of rescue treatment and until platelet counts fell lower than 50x10^9/L after ceasing rescue treatment.

The primary outcome in Kuter 2008 was a durable platelet response defined as weekly platelet responses (platelet counts ≥50X10^9/L)[60;64;65] during six or more weeks of the last eight weeks of treatment. Patients who received rescue medications at any time during the study could not be counted as having a durable response. These primary outcomes were not similar enough to be directly compared.

Kuter 2008 also reported overall (durable plus transient) platelet response as a secondary outcome, with transient response defined as four or more weekly platelet responses, without a durable response, from week 2 to 25 of therapy[60;64;65].

To facilitate an indirect comparison with durable and overall response in Kuter 2008 the post hoc analysis of RAISE carried out on the intention to treat population, was used (see Section 5.5.3 for results of this analysis). It is important to note that these end points were not pre-specified in RAISE.For simplicity the sustained response in RAISE is referred to as “durable” as these two endpoints were compared in the indirect treatment comparison. The post hoc analysis, and therefore interpretation of the indirect treatment comparison of response rates, is limited by the following:

Differences in trial designs

After the initial 6 weeks of the trial, patients with a stable platelet count could be assessed monthly in RAISE. Weekly assessments were conducted in Kuter 2008. In order to estimate durable and overall response using the definitions in Kuter 2008,

the RAISE post hoc analysis applied an assumption that patients remain at the same platelet level as their previous assessment.

- The trial protocols differed in their allowance of dose reduction or discontinuation of concomitant ITP medications:
  - RAISE did not allow tapering of concomitant ITP medication during the first six weeks of treatment but did allow and encouraged this beyond six weeks in patients with platelet counts ≥100x10^9/L. Dose reductions of ITP medications are inherently associated with fluctuation in platelet counts. Kuter 2008 only allowed dose reduction or discontinuation of ITP medications during the first 12 weeks of treatment, so platelet counts were less likely to fluctuate during the last 12 of weeks of the study[60;64;65]. This may have affected the post hoc analysis of durable and overall response, given that at the time when platelet counts for these analyses were measured, RAISE was encouraging reductions in concomitant ITP medication dose.
- Platelet counts >400x10^9/L are not considered responses in the RAISE post hoc analysis of durable and overall response, but were in the original Kuter 2008 analysis. This would likely bias against eltrombopag in the indirect comparison.
- A period of rescue medication was considered to be on-going until the platelet count returned to <50x10^9/L in the RAISE post hoc analysis, but was assumed to continue for 8 weeks in Kuter 2008[60;64;65]. The direction of bias caused by this difference is not known.
- The definition of transient response in RAISE required four *consecutive* responses, as opposed to four or more weekly responses in Kuter 2008[60;64;65]. This would likely introduce bias against eltrombopag in the indirect comparison given that in a disease with inherently fluctuating platelet counts it is more challenging to attain 4 *consecutive* platelet counts beyond a specified target.

Concomitant medications and discontinuation

A greater proportion of patients received concomitant ITP medication at baseline in RAISE compared to Kuter 2008. There was a high rate of discontinuation of concomitant ITP medications within the RAISE trial (percentage of patients who reduced/discontinued ≥1 baseline ITP medication: 59% in the eltrombopag arm, 32% in the placebo arm), which may bias against eltrombopag in the indirect comparison.

Bleeding event definitions

RAISE incorporated two methods of collecting bleeding data: proactive collection at study visits, using the WHO bleeding scale, and bleeding adverse events reporting by physicians, using the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) scale. The latter were classified as safety data. Kuter 2008 collected bleeding data only via adverse event reporting (also classified as safety data), using an unnamed scale that appears to be analogous to the CTCAE scale (see Section 5.7.4).

In view of the fact Kuter 2008 did not collect WHO bleeding scale data, it seems most appropriate that a comparison of bleeding in patients receiving eltrombopag versus those receiving romiplostim should concentrate solely on events reported using the CTCAE scale in both trials. The post-hoc nature of these analyses, along with the fact that the scale reported by Kuter 2008 may not have been the exact CTCAE scale, should be considered when interpreting the evidence. The only data publicly available for romiplostim are per patient bleeding rates, as reported in Tables 28 and 29 of the 2009 romiplostim EPAR[76], therefore eltrombopag per patient data from the RAISE trial was used in the comparison with romiplostim.

5.7.8 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

An indirect comparison was performed using the Bucher method[77]. This method maintains the randomisation from each trial and compares the relative treatment effects across trials on a chosen scale.

For this method to be valid a number of assumptions are required:

- Common comparator: In this case placebo.
- Homogeneity (in underlying meta-analyses): Cannot be assessed due to limited number of studies (the two Kuter studies) in this analysis (regression as opposed to Mantel-Haenszel approach made little difference to the results, see below).
- Generalisability: The populations in RAISE and Kuter can be considered broadly comparable.
- Consistency: No direct evidence comparing eltrombopag and romiplostim is available to validate this assumption.

Results from the Kuter 2008 studies were pooled (Mantel-Haenszel meta-analysis) for this analysis. A logistic regression model used to estimate the odds ratio for durable and overall response of romiplostim compared to placebo for all patients (reference ERG report for original eltrombopag submission) made little difference to the outcome of the subsequent indirect treatment comparison. It is also debatable as to whether regression methods are warranted to adjust for potential treatment effect modifiers in the presence of only two trials and one treatment effect parameter (splenectomy status). This approach is not discussed further.

The indirect treatment comparison is based on the post hoc analysis of durable and overall response rates using data from the ITT population (GSK Data on File, 2011). Table B36summarises the RAISE and Kuter response data used in this analysis. Zero events/empty cells were addressed by the addition of 0.5 to all cells in the trial.

The results of the indirect comparisons of platelet response and bleeding events (eltrombopag compared with romiplostim; Bucher method), are presented in Table B37 and Table B39.

5.7.9 Please present the results of the analysis.

Indirect comparison of durable response and overall response: results

Data used for the indirect comparison of durable and overall response is provided in Table B36.

Table B36 Durable and overall response data from RAISE and Kuter 2008 used to perform indirect comparison

	RAISE Data on File, 2011 ITT population				Kuter 2008 ITT population			
	Treatment Group				Treatment Group			
	Placebo		Eltrombopag		Placebo		Romiplostim	
	n	%	n	%	n	%	n	%
N– Total population	62	-	135	-	42	-	83	-
Durable response, n (%)	4	6	63	47	1	2	41	49
Overall response, n (%)	8	13	91	67	3	7	69	83
N- Splenectomised	21	-	50	-	21	-	42	-
Durable response, n (%)	1	5	20	40	0	0	16	38
Overall response, n (%)	2	10	30	60	0	0	33	79
N– Non-splenectomised	41	-	85	-	21	-	41	-
Durable response, n (%)	3	7	43	51	1	5	25	61
Overall response, n (%)	6	15	61	72	3	14	36	88

As Table B37 shows, the odds ratio for all patients of achieving a durable response is 0.32 (95% CI: 0.03, 3.14), and the odds ratio of achieving an overall response is 0.22 (0.05, 1.02), for eltrombopag versus romiplostim. The confidence intervals are very wide and cross 1.0 (no evidence of significant differences) in all cases. These trends are maintained when the data are stratified according to splenectomy status.

Table B37 Indirect comparison of platelet response rates[73]

	Indirect comparison eltrombopag versus. romiplostim (odds ratio, 95% CI)	
	Durable response	**Overall response**
All subjects	0.32 (0.03, 3.14)	0.22 (0.05, 1.02)
Splenectomised subjects	0.50 (0.01, 17.32)	0.09 (0.00, 2.52)*
Non-splenectomised subjects	0.41 (0.04, 4.80)	0.34 (0.06, 2.14)

***** This result varies from that in the public domain as an inconsistency in the handling of zero events was identified and has been corrected

Indirect comparison of bleeding events: results

The romiplostim European Public Assessment Report (EPAR) reports the subject incidence of bleeds in patients receiving placebo and those receiving romiplostim, for either grades 2-5 or grades 3-5[76]. As the incidence of bleeds is presented in total for these groups and not separately for each grade, the eltrombopag data have been grouped similarly (see Table B38).

Table B38 Incidence of bleeding events - CTCAE TRA 102537 RAISE and 5-point scale Kuter 2008

All patient	Eltrombopag			Placebo			Romiplostim			Placebo		
	n	N	%	N	N	%	n	N	%	n	N	%
Bleeding grade 2-5	12	135	8.9	9	62	14.5	13	84	15.5	14	41	34.1
Bleeding grade 3-5	3	135	2.2	4	62	6.5	6	84	7.1	5	41	12.2
Splenectomised	**Eltrombopag**			**Placebo**			**Romiplostim**			**Placebo**		
	n	N	%	N	N	%	n	N	%	n	N	%
Bleeding grade 2-5	4	50	8.0	4	21	19.0	9	42	21.4	8	21	38.1
Bleeding grade 3-5	0	50	0.0	2	21	9.5	4	42	9.5	4	21	19.0
Non-splenectomised	**Eltrombopag**			**Placebo**			**Romiplostim**			**Placebo**		
	n	N	%	n	N	%	n	N	%	n	N	%
Bleeding grade 2-5	8	85	9.4	5	41	12.2	4	42	9.5	6	20	30.0
Bleeding grade 3-5	3	85	3.5	2	41	4.9	2	42	4.8	1	20	5.0
Source of data:	RAISE CSR (Table 49 cross-referenced with listing 2; data on file)						Romiplostim EPAR (Tables 28 and 29)					

Six indirect comparisons were conducted: grade 2-5 and grade 3-5 bleeds were analysed amongst all patients and amongst splenectomised and non-splenectomised patients. In some analyses the point estimates favour eltrombopag, and others favour romiplostim, however none showed statistically significant differences in the risk of bleeding between the treatments which suggests no evidence of a difference in efficacy (Table B39).

Table B39 indirect comparison of bleed rates[73]

	Indirect comparison romiplostim versus. eltrombopag* (relative risk, 95% CI)	
	Grade 3-5 bleeds**	**Grade 2-5 bleeds****
All subjects	1.70 (0.27, 10.81)	0.74 (0.26, 2.10)
Splenectomised subjects	5.80 (0.22, 150.71)	1.34 (0.29, 6.09)
Non-splenectomised subjects	1.32 (0.07, 24.47)	0.41 (0.09, 1.95)

*Relative risk=$P_{exposed}/P_{non\text{-}exposed}$

** Common Toxicity Criteria for Adverse Events (CTCAE) scale

Summary of findings

The indirect comparison found no significant differences between the two treatments.

RAISE and Kuter 2008 used similar inclusion criteria and recruited similar patient populations. The differences in baseline patient characteristics are largely attributable to differences in trial designs and local standards of care, the heterogeneous nature of the refractory cITP population, and the relatively small patient numbers.

The indirect comparison provided limited information on the relative efficacy of the treatments. The confidence intervals around the estimated treatment effects are wide and cross 1.0 (no evidence of significant differences) in all cases. The point estimates favoured both treatments depending on the end point assessed. In

addition to this uncertainty a number of potential biases may be affecting the indirect comparison:

1. Imbalances between the placebo and romiplostim arms of Kuter 2008, identified by the FDA (See Section 5.11 for the comparative efficacy of romiplostim and eltrombopag), may have impacted the indirect comparison
   - Additional analyses described in section 6.10.4 demonstrate the instability of the results of the indirect treatment comparison and its sensitivity to the event rate in the placebo arm of the Kuter studies.
2. Differences in the trial protocols with respect to concomitant therapy adjustments led to reductions in concomitant therapy use in RAISE during the period when durable and transient response were measured, which may have biased the indirect comparison against eltrombopag.

The pivotal trials for eltrombopag and romiplostim showed that both compounds are highly effective when compared to their respective placebo control arms.

The indirect comparison of eltrombopag and romiplostim, does not provide evidence of a significant difference between the two treatments, the level of uncertainty and potential biases in the comparison and the fact that two independent, recently issued international clinical guidelines do not favour one treatment over the other, the base case analysis for the cost-effectiveness model assumes that the treatments offer equal efficacy.

5.7.10 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

Sources of heterogeneity between and within the patient populations of RAISE and Kuter 2008, and differences in trial designs, are discussed in Section 5.7.6 and Section 5.7.7.

No statistical adjustment was conducted for potential treatment effect modifiers. Adjustment using meta-regression is not possible in the presence of two trials and two treatment effect parameters as there is insufficient data with which to estimate any treatment effect modification.

An alternative approach would have been to explore the effect of baseline characteristics on treatment effects within RAISE. However, more robust conclusions on the basis of an assessment of these types of interaction effects would be unlikely, given the relatively small patient numbers.

5.7.11 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

Not applicable

5.7.12 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

Not applicable

5.8 Non-TPO-RA Indirect comparison

5.8.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.4, appendix 4.

Evidence for non-TPO-RA treatments was retrieved using the same search strategies as previously outlined for the identification of eltrombopag and romiplostim studies. The following treatments, named in the international consensus guidelines[7] were selected for inclusion: IVIg, Anti-D, rituximab, corticosteroids, vina alkaloids, mycophenolate mofetil, cyclosporine, cyclophosphamide, danazol and dapsone.

There have been no new publications for azathioprine in the treatment of ITP.

Full details of the search strategies used to identify appropriate studies are provided in Section 5.2 and Appendix 2.

5.8.2 Please follow the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 9.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Section 5.2 provides details of study selection. A total of 108 studies were identified reporting non-TPOs, including 18 RCTs.

A brief summary of the randomised evidence identified by the systematic review is provided as Table B40. There is relatively little high quality data for non-TPO-RA treatment in cITP, and the reporting varies considerably between the studies.

The randomised evidence takes the form of comparisons (or dose comparisons) of treatments that would most likely be considered as a rescue option rather than as a maintenance treatment in the population considered in this appraisal. Four RCTs have compared rituximab to steroid treatment: only one of these was restricted to patients who had received prior ITP treatment, and this study was small (n=62) and carried out in an Asian population.

Table B40 Summary of all randomised evidence retrieved by systematic review

Study type	Reference and comparison	Relevance of comparison
Comparison of rescue therapies or steroids	**Bae ASH 2010[78]:** prednisolone versus. dexamethasone **Bellucci 1988[79]:** prednisone dose comparison **Borte 2004[80]:** comparison of IVIg types **Bussel 2004[81]:** comparison of IVIg types **Colovic 2003[82]:** comparison of IVIg dosages **Ferrari 1991[83]:** prednisone versus. deflazacort **George 2003[84]**: Anti-D versus. prednisone **Godeau 1993[85]:** comparison of IVIg dosages **Godeau 1999[86]:** comparison of IVIg dosages **Godeau 2002[87]:** IVIg + oral prednisone versus. HDMP + oral prednisone versus. IVIg versus. HDMP **Jacobs 1994[88]:** oral prednisolone versus. IVIg versus. oral prednisolone + IVIg **Mazzucconi 1985[89]:** prednisone dose comparison **Newman 2001[90]:** Anti-D dose comparison **Praituan 2009[91]**: prednisolone versus. dexamethasone **Shen 1995[92]:** prednisone versus. prednisone + heparin	Limited relevance, these treatments are typically used as rescue treatments in the population of interest. Additionally, Bae ASH 2011 and Jacobs 1994 reported newly diagnosed patients.
Comparison of rituximab to steroids	**Arnold 2011[93]:** rituximab + standard therapy versus. standard therapy **Gudbrandsdottir 2010[94]:** dexamethasone or prednisone + rituximab versus,. dexamethasone or prednisone **Li 2011[95]**: dexamethasone or prednisone + rituximab versus,. dexamethasone or prednisone **Zaja 2008[96]:** rituximab + dexamethasone versus. dexamethasone	Limited relevance. Gudbrandsdottir 2010 and Zaja 2008 all conducted in newly diagnosed patients/previously untreated patients, Arnold 2011 also allowed newly diagnosed patients.
Comparison of unconventional use of rituximab	**Hasan 2009[97]:** R-CVP versus. double-dose rituximab	Regimens not typically used in ITP treatment.

HDMP: High Dose Methylpredisolone R-CVP: Rituximab, Cyclophosphamide, Vincristine, Prednisolone

In the absence of relevant RCT data for the non-TPO-RA treatments, the evidence synthesis approach used in the model takes the form of a naïve indirect comparison of individual trial arms. Trials are summarised by comparator, rather than pairwise comparison, as the majority of the evidence is from single arm studies.

Extent of reporting, patient populations and outcome definitions differed considerably across the included studies. In order to provide data that was more comparable to the study design and population of RAISE[38;39], the following additional criteria were used to select studies from the systematic review for inclusion in the discussion and analysis:

- Baseline characteristics
  - Studies with a reported inclusion criteria of platelet counts ≤30x10^9/L. If studies did not specify the platelet level required for patient inclusion they were included if the average (mean or median) baseline platelet count was ≤20x10^9/L
  - Prior ITP medications reported. If a study stated that any of the included patients had received prior ITP medications the study was included. If the use of prior medication was not reported or no patients had received prior treatment, then the studies were excluded.
- Studies which reported the following outcomes:
  - Response as a platelet count of >50 X10^9/L, or
  - Time to response , or
  - Duration of response

Given the limited reporting of time to response and duration of response, all reported data was included in the analysis regardless of the definition of response. For included studies any additional outcomes reported were also extracted. If mutually exclusive responses were reported, but cumulatively provided the response of >50x10^9/L (i.e. platelet counts of 50-100X10^9/L and >100X10^9/L were reported) then these response rates were combined in both the data extraction and synthesis to generate a ≥50X10^9/L response rate.

Implementation of the criteria above resulted in a large number of studies identified in the systematic review being excluded from the analysis (79[3] out of 116). The studies included for further discussion and analysis are summarised in Table B41. The high rate of exclusion of trials reflects both poor quality reporting, and the paucity of data in refractory patients with low platelet counts.

Where sufficient data was identified the weighted averages for response, time to response and duration of response was calculated (details of data used is provided in appendix 4). Further details of these calculations are provided in section 5.8.12.

Additional outcomes reported in these studies, including bleed rates and adverse events, are not reported here as the reporting of these endpoints was minimal.

[3] If at least one arm of a study was included, then this was counted as an included study.

5.8.3 **Identified Non-TPO studies**

Included non-TPO-RA studies are summarised in Table B41. Full details of the baseline characteristics, prior and concomitant ITP medication use and time to response and duration of response outcomes are provided in Appendix 4.

A brief summary of the findings for each treatment is given in this section. In addition, any response outcomes reported by splenectomy status are outlined in section 5.8.10.

Table B41 Non-TPO-RA studies identified from both systematic reviews included in analysis

References of trials	IVIg	Anti-D	Rituximab	Vinca Alkaloids	Corticosteroids	Other*
Alasfoor, 2009[98]			●			
Aledort, 2007[99]		●				
Borte, 2004[80]	●					
Bussel, 2004[81]	●					
Colovic 2011[100]						●
Cooper, 2004[101]			●			
Garcia- Chavez, 2007[102]			●			
Godeau, 1993[85]	●					
Godeau, 1993[103]						●
Godeau, 2008[104]			●			
Gomez-Almaguer 2010[105]			●			
Gringeri, 1992[106]		●				
Gutierrez-Espindola, 2003[86]					●	
Hasan 2009[97]			●			
Hernandez, 1995[107]						●
Hou, 2003[108]						●
Julia 2009[109]	●					
Kim, 2005 [Abstract][110]					●	
Kueh, 1982[111]				●		
Li 2011[95]			●		●	
Medeot, 2008[112]			●			
Montes-Gaisan, 2009 [Abstract][113]			●			
Nalli, 1988[114]						●
Pasa, 2009[115]			●			
Peñalver, 2006[116]			●			
Praituan 2009[91]					●	
Provan, 2006[117]						●
Reiner, 1995[118]						●
Robak 2009[119]	●					
Robak 2010[120]	●					
Santaro, 2006 [Abstract][121]			●			
Scaradavou, 1997[122]		●				
Stasi, 2000[123]					●	
Stasi, 2001[124]			●			
Varga, 2006[125]	●					
Yassin, 2011 [Abstract][126]			●			
Zaja, 2003[127]			●			

*Includes cyclophosphamide, danazol, dapsone and mycophenolate mofetil

5.8.4 IVIg

Details of studies retrieved relating to IVIg are shown in Appendix 4. Seven studies were retrieved, including three RCTs comparing the efficacy of different IVIg medications or doses[80;81;85]. The number of participants in each study arm ranged from 9 to 115. Duration of ITP ranged from an average of six months to 7.5 years, however a maximum of less than 24 years was reported in Borte 2004. Baseline platelet counts ranged from $9.6x10^9$/L to $19x10^9$/L. Duration of treatment ranged from two days to five days, with the follow up periods ranging, on average, from 21 days to 3 months; however Godeau 1993 reported a maximum 66 months follow up[85].

The most commonly reported prior treatments were corticosteroids and splenectomy. The use of concomitant ITP medication was reported in four studies.

Table B42 shows response outcomes reported for treatment with IVIg. Responses (>50x109/L) were observed in 70-100% of patients and the weighted average calculated was 82%. Time to response was 2 to 6 days. Duration of response was reported in only four papers, with an average (mean or median) duration ranging from 6 to 15.4 days. The weighted average of the time to response was 3.5 days and the durability of response was 17.2 days (weighted mean).

IVIg is commonly regarded as a first-line or rescue treatment for patients with ITP, because, while it produces a rapid increase in platelet count, the duration of response is short lived.

Table B42 Response outcomes of IVIg studies

Reference	Treatment Arm	N	Response category	Definition of response (platelet count x10^9)	Result	Durability of response	Definition of Durability of response (x10^9)	Time to response	Definition of time to response
Borte, 2004[80]	IvIG-F10	16	NR	NR	NR	6 days	Mean	5 days (3–15)	mean
	Sandoglobulin	17	NR	NR	NR	10 days	Mean	4 days (2–8)	mean
Bussel, 2004[81]	IvIG-C, or S/D 2 g/kg, (1 g/kg/day)	61	Responder rate	>50	day 7: 55/61 (90%)	NR	NR	NR	NR
Godeau, 1993[85]	IvIG, 2 g/kg	9	Response	>50	9 (100%)	NR	NR	6 days (4–11)	mean
Varga, 2006[125]	IVIg	23	Response	>50	17 (73.9%)	NR	NR	NR	NR
Julia 2009[109]	Flebogammadif	20	Response	Platelet count of ≥ 50 at any time during the study period	14 (70%)	≥ 14.3 days	Mean time from the first measurement of a platelet count ≥ 50 to the last measurement above or equal to that level	(n=14) ≤ 2.5 days	Median time to platelet response from first dose
		8	Response	Response in splenectomised patients	5	≥ 7 days	Median time from the first measurement of a platelet count ≥ 50 to the last measurement above or equal to that level	(n=14) ≤ 9.5 days	Mean time to response from first dose
Robak 2009[119]	Privigen	57	Platelet response	≥ 50 within 7 days of first privigen infusion	46 (80.7%)	15.4 days (1 to >82 days)	Median (range) duration for patients who achieved a	2.5 days	Median time to attain response after starting

Reference	Treatment Arm	N	Response category	Definition of response (platelet count x10^9)	Result	Durability of response	Definition of Durability of response (x10^9)	Time to response	Definition of time to response
							response at any point		privigen administration
Robak 2010[120]	Octagam	115	Clinical response	an increase in platelet count to ≥ 50 within 6 days of dosing	92 (80%) [95% CI 72.7%; 87.3%]	12 days (1 to 79)	Median duration of response with a count only of the number of days up to the last visit at which the count remained ≥50	2 days (1 - 6)	Median time to response in responding patients.

SD: Solvent detergent; NR: Not reported

5.8.5 Anti-D

Anti-D is not licensed in the UK for treatment of ITP. Details of the three studies retrieved reporting the use of Anti-D are shown in Appendix 4. Number of participants in each study arm ranged from 27 to 137, with duration of ITP ranging from 6 months to 2.3 years. Where reported, the baseline platelet count ranged from 14.3 to $15x10^9$/L. The duration of treatment ranged from a single dose of Anti-D on day 1, to between three and six days. The follow up period ranged from 29 days to 6 months. Scaradavou 1997 was the only study to provide details of concomitant ITP medication use, reporting that tapering of concomitant medication doses was allowed if responses to Anti-D were seen[122]. All studies provided details of prior ITP medications used, with the use of corticosteroids being reported most often.

The response outcomes for Anti-D studies are shown in Table B43. Responses were observed in between 34% and 52.7% of participants. The weighted average of response was 42%. Time to response and duration of response were not reported in any of the studies.

Table B43 Response outcomes for Anti-D studies

Reference	Treatment Arm	N	Response category	Definition of response (platelet count $x10^9$)	Result
Aledort, 2007[99]	Anti-D Single IV injection: 50 µg/kg bodyweight	98	Response Rate	≥50	49/93 (52.7%)
Gringeri, 1992 [106]	Anti-D idiopathic chronic ITP patients	27	Response Rate	>50	14/27 (52%)
Scaradavou, 1997[122]	First subjects enrolled treated with daily doses. Subsequent subjects received single IV dose	137	Response	≥50	46/137 (34%)

5.8.6 Rituximab

Fifteen studies on treatment with rituximab were identified, including two RCTs. Full details are given in Appendix 4. One RCT compared the efficacy of a high dose of rituximab to rituximab in combination with chemotherapy[97] and one compared rituximab to corticosteroid treatment of dexamethasone followed by prednisone[95].

Number of participants in the study arms ranged from 8 to 89, with average duration of ITP between 13 and 127 months. The baseline platelet count ranged from $5.5x10^9$/L to $19.5x10^9$/L. Most studies reported weekly treatment for 4 weeks, but a treatment schedule lasting 6 weeks was reported in Yassin 2011[126]. Average follow up ranged from 6 to 56.5 months.

There was more detail of prior ITP medication use than in other non-TPO-RA studies. Most of the studies did not report the use of concomitant ITP medications; of the two that did, Gomez-Almaguer 2010 allowed use of a variety of ITP therapies[105], and Li 2011 did not allow use of concomitant ITP medications[95].

The reported outcomes of the included rituximab studies are shown in Table B44. Responses of over $50x10^9$/L were observed in between 14% and 93% of patients, the average time to response was between 4 and 14 weeks, and the duration of response was 12.5 to 56 months. The weighted average for response was 59%[4], and average time to response and average duration of response were 24 days (3.4 weeks) and 748 days (107 weeks), respectively.

[4] Using only the 1 year response rate from Godeau 2008 as this is closest to the follow up period of RAISE. Additionally, although Yassin 2011 reported response, this was defined as 50 – $100x10^9$/L for more than six months, and as >$100x10^9$/L for more than a year. As the definitions were non comparable the response rates could not be combined for inclusion in the analysis

Table B44 Response outcomes for rituximab studies

Reference	Treatment Arm	N	Response category	Definition of response (platelet count x10^9)	Result	Durability of response	Definition of Durability of response (x10^9)	Time to response	Definition of time to response
Alasfoor, 2009[98]	IV Rituximab, 375 mg/m2, weekly	14	Complete response	>50	13 (93%)	12.5 (2-19) months	median	NR	NR
Cooper, 2004[101]	IV Rituximab, 375 mg/m2, weekly	57	Response	>50	31 (54%)	NR	NR	NR	NR
Garcia-Chavez, 2007[102]	IV Rituximab, 375 mg/m2, weekly	18	Complete response	>50	10 (56%)	NR	NR	14 weeks (4-32)	median time
Godeau, 2008[104]	IV Rituximab, 375 mg/m2, weekly	60	Good Response at 1 year	>50 with a 2 fold increase of inclusion value	24/60 (40%)	NR	NR	NR	NR
		60	Good Response at 2 years		20/60 (33.3%)	NR	NR	NR	NR
Medeot, 2008[112]	IV Rituximab, 375 mg/m2, weekly	26	Complete response	≥ 50, discontinuation of steroid therapy	18/26 (69%)	21 months	median	NR	
Pasa, 2009[115]	IV Rituximab, 375 mg/m2, weekly	17	Response rate	>50	10 (64.7%)	NR	NR	11 weeks (2–13)	median time to response
Peňalver, 2006[116]	IV Rituximab, 375 mg/m2, weekly	89	Response	≥50	49/89 (55.1%)	NR	NR	NR	NR
Santaro, 2006 [121]	IV Rituximab, 375 mg/m2, weekly	14	Response	>50	6 (43%)	NR	NR	NR	NR
Stasi, 2001[124]	IV Rituximab, 375 mg/m2, weekly	25	Response	>50	10 (40%)	NR	NR	NR	NR
Zaja, 2003[127]	IV Rituximab, 375 mg/m2, weekly	37	Overall response	≥50	27/37 (73%)	NR	NR	NR	
Gomez-Almaguer 2010[105]	Alemtuzumab plus Rituximab	11	Partial response	Platelet count ≥ 50 on 2 consecutive occasions	6 (55%)	46 weeks (16-88)	median (range) duration of complete	1 week	time to achieve a response

Reference	Treatment Arm	N	Response category	Definition of response (platelet count x10^9)	Result	Durability of response	Definition of Durability of response (x10^9)	Time to response	Definition of time to response
							response		
Li 2011[95]	Dexamethasone/ prednisone + rituximab	31	Overall response	Complete response or partial response at 28 days (>50)	80.6%, (p= 0.938‡)		NR	NR	
		31	Sustained response rate	Platelet count ≥50 at month 6 after initial treatment	24 (77.4%) p<0.001‡				
Hasan 2009[97]	Rituximab-CVP	8	Response	CR (>150) or PR (>50) each lasting >3 months	3 (38%)		NR	NR	
	Rituximab-DDR	8	Response	CR (>150) or PR (>50) each lasting >3 months	5 (63%)		NR	NR	
Montes-Gaisan, EHA 2009[113]	Rituximab	17	Complete remission	Platelet count >50	14 (82%)	NR	NR	4 weeks (1-8)	Median time from first rituximab dose to any response
		NR	Relapse rate	Remission rate when rituximab was used as second or third line	91%				
		NR	Relapse rate	Remission rate when rituximab was used as fourth line	67%				
		NR	Relapse rate	Relapsed beyond 12 months of follow-up	4/14 (28%)				
		NR	Relapse rate	Remission in patients older than 18 years	100%				
Yassin,	Rituximab	14	No response	NR	2 (14%)	28 months	Mean		

Reference	Treatment Arm	N	Response category	Definition of response (platelet count x10^9)	Result	Durability of response	Definition of Durability of response (x10^9)	Time to response	Definition of time to response
EHA 2011[126]							complete response		
		14	Partial response	Platelet count 50-100 for more than 6 months	2 (14%)				
		14	Complete response	Platelet count > 100 for more than one year	12 (86%)				

‡p value versus dexamethasone/prenisone (seeTable B47); NR: not reported; CVP: cyclophosphamide, vincristine, prednisolone; DDR: double dose rituximab

5.8.7 Vinca alkaloids

Only one small study was identified for vinca alkaloids (vincristine) which met all of the previously stated inclusion criteria. Details are given in Appendix 4. The study included 12 participants, with an average baseline platelet count of $12x10^9$/L. A maximum of three weekly infusions was allowed, and the duration of follow up was approximately 10 weeks. Participants included had been diagnosed with ITP for, on average, 18 months. The only previous treatments received for ITP outlined was splenectomy (n=2). Use of concomitant medication was not reported.

The response outcomes are reported in Table B45. Response of over $50x10^9$/L was reported in 59% of patients. No time to response or duration of response outcomes were reported.

Table B45 Response outcomes of included vinca alkaloid studies

Reference	Treatment Arm	N	Response category	Definition of response (platelet count $x10^9$)	Result
Kueh, 1982[111]	Bolus vincristine, 1 mg	12	Overall response: [response observed within first week of treatment]:		8/12 (67%)
		12	Response	>50	7/12 (59%)

no time to response or durable response outcomes were reported

5.8.8 Other treatments

Details of baseline characteristics and previous and concomitant medications for the studies identified are given in Appendix 4. Response outcomes are shown in Table B46.

5.8.8.1 Danazol

One relevant danazol study was identified (Nialli 1988[114]), which included 14 participants divided into two groups: patients refractory to corticosteroids only and patients refractory to multiple treatments. Duration of ITP was not reported. Baseline platelet count was between 2 and $52x10^9$/L in both groups[5]. Treatment was administered for two months, and patients were followed up for 12 months. The study was split into two groups: patients refractory to corticosteroids and patients refractory to multiple treatments. The use of concomitant ITP medications was not reported.

The response rate (>$50x10^9$/L) sustained for 2 months observed in Nalli 1988 was 35%, with a sustained response over 12 months observed in 21% of participants. Time to response and duration of response were not reported[114].

[5]Group B of Nailli 1988 had a range of 10-38X10^9/L. As no other Danazol studies had been identified meeting the platelet criteria criteria (<30X10^9/L, or mean/median <20X10^9/L) this study was included given that it seemed likely that the median/mean could be below 20 X10^9/L.

5.8.8.2 Cyclophosphamide

Only Reiner 1995 reported on cyclophosphamide treatment[118]. This study included 20 participants who had been diagnosed with ITP for, on average, 6 months and whose average baseline platelet count was $7x10^9$/L. Treatment duration averaged 2 months, and patients were followed up for 2.5 years. All patients had received prior corticosteroids, and 19 of the 20 had been splenectomised. Use of concomitant medication was not reported.

A response rate (>$50x10^9$/L) of 85% was observed. Time to response and duration of response were not reported.

5.8.8.3 Dapsone

The use of dapsone was reported in two studies, which included 15 and 21 participants. Average ITP duration was 13 and 29 months and baseline platelet counts were 16 and $22x10^9$/L. Only Hernadez 1995 reported duration of treatment (12 weeks), and neither study reported the follow up period[107]. Both studies reported a number of different prior medications; neither reported on concomitant medication use.

Responses (>$50x10^9$/L) were observed in 40% and 48% of participants, with the weighted average indicating a response of 45%. Time to response was reported as 30 days in Godeau 1993[103], and the majority of responders in Hernandez 1995 had also responded by one month (Table B46). The weighted average time to response was 35.4 days[6]. Duration of response was not reported.

5.8.8.4 Mycophenolate mofetil

The use of mycophenolate mofetil was reported in three studies. The number of participants in the study arms ranged from 16 to 21. Duration of ITP was 28 months to 9 years and baseline platelet counts ranged from 8 to $16x10^9$/L. Duration of treatment was 12 to 37 weeks, and patients were followed up for between 22 and 78 weeks. Participants were heavily pre-treated with a variety of treatments. None reported concomitant ITP medication use.

The response rates ranged from 39% to 69% (weighted average 53%). The time to response was not reported in any of the studies. Durability of response was reported in Provan 2006, where a response of >$30x10^9$/L was observed on average for five weeks[117].

[6] Godeau 1993 could not be used for the weighted average calculation as it was not stated whether the value reported represented the mean or median

Table B46 Response outcomes of studies including cyclophosphamide, danazol, dapsone and mycophenolate mofetil

Reference	Treatment Arm	N	Response category	Definition of response (platelet count $x10^9$)	Result	Durability of response	Definition of Durability of response ($x10^9$)	Time to response	Definition of time to response
Reiner, 1995[118].	High dose cyclophosphamide 1.0-1.5g/m2, rapid iv infusions, repeated at 4-week intervals Mean number of doses : 2 (1-4)	20	Response	≥50	17 (85%)	NR	NR	NR	NR
Nalli, 1988[114].	Danazol 200mg TID	14	Response	>50 (sustained for at least 2 months)	5 (35%)	NR	NR	NR	NR
			Sustained response	>12 months	3 (21%)				
Godeau, 1993.[103]	Dapsol 100mg/day oral	27	Response	>50	13 (48%)	NR	NR	30 days (12-120)	Duration of treatment required to achieve $50x10^9$/L
		27	No Response		12 (44%)				
Hernandez, 1995.[107]	Dapsol 100mg/day	15	Complete response	>50 (sustained for at least 2 months)	6 (40%)	NR	NR	Time to response was one month (n=5) and 2 months (n=1)	
Hou, 2003.[108]	Mycophenolate mofetil1.5–2 g/day	21	Response:	>50 (sustained for at least 2 months)	11 (53%)	NR	NR		
Provan, 2006.[117]	Mycophenolate mofetil 250–1000 mg bd	18	Sustained response	Sustained platelet increase >50	7 (39%)	5 (0–24)	No of consecutive weeks with platelet count	NR	NR

Reference	Treatment Arm	N	Response category	Definition of response (platelet count x10^9)	Result	Durability of response	Definition of Durability of response (x10^9)	Time to response	Definition of time to response
							>30		
Colovic 2011[100]	Mycophenolate mophetil	16	Response	Complete response and partial response (>50)	11 (69%)	NR	NR	NR	NR
		9	Response	Complete response and partial response in splenectomised patients	6 (67%)				
		7	Response	Complete response and partial response in non-splenectomised patients	5 (71%)				

NR: Not reported

5.8.9 Corticosteroids

Five studies were identified reporting the use of corticosteroids that matched the pre-stated inclusion criteria. Only one RCT was included, Li 2011[95], which compared the efficacy of dexamethasone followed by prednisone to rituximab (see Section 5.8.6 for results). Kim 2005 was a two arm open label study which compared a treatment naïve group to a relapsed group[110]; only the outcomes of the relapsed group are reported here. The corticosteroids used include prednisone, prednisolone and dexamethasone.

Baseline characteristics and prior and concomitant medications are shown in Appendix 4. All studies reported prior ITP medications, and two reported concomitant ITP medications.The number of participants in each study arm ranged from 17 to 62, with the average duration of ITP ranging from 3 to 23.5 months. Baseline platelet counts ranged from 6 to $24x10^9/L$[7]. Treatment duration ranged from 4 days to 6 months, with the duration of follow up ranging from 6 to 12 months.

Proportion achieving platelet response outcomes of $>50x10^9/L$ varied from 35% to 88%. The weighted average estimated that 54% of participants would respond to corticosteroids. No studies reported time to response or response duration.

[7] Gutierrez-Espinodola 2003 reported baseline platelet count according to splenectomy status, splenectomised = $17x10^9/L$ and non-splenectomised = $24x10^9/L$

Table B47 Response outcomes of corticosteroid studies

Reference	Treatment Arm	N	Response category	Definition of response (platelet count x10^9)	Result
Gutierrez-Espindola, 2003.[128]	Total Patients 40 mg high dose dexamethasone infused every 24 hours for 4 consecutive days. Cycle repeated every 28 days until completion of six cycles	19	Favourable response	≥50	8 (42%)
	Splenectomised: 40 mg high dose dexamethasone infused every 24 hours for 4 consecutive days. Cycle repeated every 28 days until completion of six cycles	8	Favourable response	≥50	6 (75%)
	Non-splenectomised: 40 mg high dose dexamethasone infused every 24 hours for 4 consecutive days. Cycle repeated every 28 days until completion of six cycles	11	Favourable response	≥50	2 (18%)
Kim, 2005.[110]	Dexamethasone, 40 mg/day for 4 consecutive days	17	Good Initial response	increase in platelet count of 30, or a platelet count of >50	6 (35%)
		17	Relapsed		2 (33.3%)
Stasi, 2000[123]	Dexamethasone, 40 mg/day for 4 consecutive days	32	Response	≥50	13 (41%)
Praituan 2009[91]	Dexamethasone	18	Satisfactory response	Mean platelet count ≥ 50 x 109/L on day 5	16 (88.8%) (p=0.001)
	Dexamethasone plus prednisolone	18	Satisfactory response	Mean platelet count ≥ 50 x 109/L on day 5	6 (33.3%)
Li 2011[95]	Dexamethasone/ prednisone	31	Overall response	Complete response or partial response at 28 days ≥50 and discontinuation of steroid therapy if present	23 (74.2%)
		31	Sustained response rate	Platelet count ≥50 at month 6 after initial treatment	12 (38.7%)

No time to response or durable response data reported in the trials.

5.8.10 Splenectomy status

Only three of the included studies provided response rates split by splenectomy status: one IVIg study, one mycophenolate mofetil study and one dexamethasone study (Table B48). In Julia 2009, 62.5% of splenectomised patients treated with IVIg responded. This compares to 70% of all patients achieving a response (splenecotomised and non-splenectomised). Splenectomised patients took longer to respond to treatment, and the duration of response was shorter than that in the whole patient population[109].

In Colovic 2011 the response rate to mycophenolate mofetil in non-splenectomised patients is 71%, compared to 67% in splenectomised patients[100].

In Gutierrez-Espindola 2003 response to dexamethasone in splenectomised patients was 75% compared to 18% in non-splenectomised patients. The population size of this study is very small (19 patients), which likely explains these anomalous results[128].

Table B48 Response outcomes of patients split by splenectomy status – all treatment comparators

Reference	Treatment Arm	N	Response category	Definition of response (platelet count x10^9)	Result	Durability of response	Definition of Durability of response (x10^9)	Time to response	Definition of time to response
Julia 2009[109]	Flebogammadif	20	Response	Platelet count of ≥ 50 at any time during the study period	n=14 (70%)	≥ 14.3 days	Mean time from the first measurement of a platelet count ≥ 50 to the last measurement above or equal to that level	(n=14) ≤ 2.5 days	Median time to platelet response from first dose
		8	Response	Response in splenectomised patients	n=5 (62.5%)	≥ 7 days	Median time from the first measurement of a platelet count ≥ 50 to the last measurement above or equal to that level	(n=14) ≤ 9.5 days	Mean time to response from first dose
Colovic 2011[100]	Mycophenolate mophetil	9	Response	Complete response and partial response in splenectomised patients (>50)	6 (67%)	NR	NR	NR	NR
		7	Response	Complete response and partial response in non-splenectomised patients (>50)	5 (71%)				
Gutierrez-Espindola, 2003.[128]	Splenectomised: 40 mg high dose dexamethasone infused	8	Favourable response	≥50	6 (75%)	NR	NR	NR	NR

Reference	Treatment Arm	N	Response category	Definition of response (platelet count x10^9)	Result	Durability of response	Definition of Durability of response (x10^9)	Time to response	Definition of time to response
	every 24 hours for 4 consecutive days. Cycle repeated every 28 days until completion of six cycles								
	Non-splenectomised: 40 mg high dose dexamethasone infused every 24 hours for 4 consecutive days. Cycle repeated every 28 days until completion of six cycles	11	Favourable response	≥50	2 (18%)				

NR: Not reported

5.8.11 For the selected trials, provide a summary of the data used in the analysis.

Weighted averages of the response rate, time to response and duration of response per treatment were calculated from the data presented above. The data used in the calculations is provided as Appendix **Error! Reference source not found.**. These results should be interpreted with caution given the generally poor level of reporting and heterogeneity both in endpoint statistics and patient populations.

5.8.12 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

Summaries of the efficacy of each comparator were performed using a naïve indirect comparison approach. Although this type of comparison is likely to be confounded by differences in patient characteristics and study design, it was deemed to be the only feasible option given the lack of relevant RCT data for many comparators. The most recent NICE appraisal in cITP (TA221) used this approach and the committee acknowledged the difficulty of providing comparative evidence against treatments unlicensed for cITP and for which the evidence base is limited[30].

Weighted averages were used for all outcomes. Data points were weighted according to the number of patients in each study. For response (a binary outcome), this is equivalent to performing a fixed effects meta-analysis. For the continuous outcomes (time to response and duration of response), weighted averages were calculated rather than performing formal meta-analysis, due to very poor reporting of any variance parameters (e.g. standard deviations, standard errors or confidence intervals). For the calculation of the weighted averages the following rules were applied to standardise the comparison:

- Response rate:
  - Response rates were only included if they referred specifically to platelet counts ≥$50x10^9$/L. If response was defined as a lower platelet count (i.e. >$30x10^9$/L) or as a higher platelet count (i.e. >$100x10^9$/L) this data was excluded.
  - Where studies reported a number of mutually exclusive response rates (i.e. 50-100, and >$100x10^9$/L) then the results from these were combined in order to provide an response of ≥$50x10^9$/L.
  - When both were reported, initial response was used rather than sustained response as initial response was more commonly and consistently reported.
  - Where additional criteria were used in the response definition (e.g. requirement for no rescue treatment, or platelet counts having to be sustained for a certain time period) these studies were included.
  - When the definition of response was not clearly stated data were not included.
- Time to response and duration of response
  - The reporting of both time to response and duration of response was both highly variable and very limited. If both mean and median duration were reported mean estimates were used. If the mean was not available the median

was used. From this the mean was then derived according to S(t)=Exp(-λt) i.e. assuming an exponential distribution. If a range of time was provided this was not included

5.8.13 Please present the results of the analysis.

Results of the weighted averages for each of the included non-TPO drugs are provided in Table B49. It is important to bear in mind that the response rates in Table B49, Table B50, and Table B51 have been informed by largely non-randomised, highly heterogenous older trials.

Table B49 Weighted averages per treatment for response, time to response and duration of response

	Total N	Response (%)	Weighted Average Time to response (days)	Duration of response (days)
Cyclophosphamide	20	85%	NR	NR
Danazol	14	36%	NR	NR
Dapsone	42	45%	3.5	NR
Mycophenolate mofetil	71	53%	NR	50.5
Anti-D	257	42%	NR	NR
IVIg	285	82%	24.4	17.2
Rituximab	463	59%	6.6	748.4
Corticosteroids	154	54%	NR	NR
Vinca alkaloids	12	58%	NR	NR

Conclusion:

cITP is an orphan disease which is highly heterogeneous and requires individualised treatment. Within the range of treatment options recommended in particular settings, guidelines acknowledge that treatment decisions are left to the discretion of both the treating physician and patient. This is partially reflective of the poor evidence base available.

The results shown in Table B49 largely reflect response rates outlined in the current guidelines (although this does not necessarily reflect their recommendations), as well as the model produced by Amgen for the romiplostim STA submission (TA221), as indicated in Table B50 and Table B51 respectively. Both the Amgen review and the current review report poorer outcomes for corticosteroids and Anti-D than are reported by the International Consensus Report[7]. The higher response rates with IVIg compared to Anti-D (82% versus 42%) may explain the preference for the former treatment as a rescue medication in the UK[33]. However, anti-D is no longer licensed for use in the UK for the treatment of ITP.

Table B50 Response outcomes per treatment as reported in the International Consensus Report[7]

	Response (%)	Time to response	Duration of sustained response
Cyclosporine	~50 - 80%	3 - 4 weeks	>50% or 2 years
Cyclophosphamide	24 - 85%	1 - 16 weeks	<50%
Danazol	67% complete/partial	3 - 6 months	46% remained in remission at median 119 months following 37 months treatment
Dapsone	<50%	3 weeks	sustained in up to two-thirds off therapy
Mycophenolate mofetil	up to 75%, complete in up to 45%	4 - 6 weeks	short term
Anti-D	initially up to 80%	4 - 5 days	typically 3 - 4 weeks, but can last longer
IVIg	initially up to 80%	2 - 4 days (can be as fast as 24h)	usually transient, lasting 2 - 4 weeks, but can last longer
Rituximab	60%, complete in 40%	1 - 8 weeks	>3-5 years in 15-20% of responders
Corticosteroids (reported as 1st line treatment)	70 - 90% in dexamethasone and prednis(ol)one	several days to several weeks	As high as 60 -80% in latter cycles of dexamethasone during 2-5 year follow-up. Remains uncertain, although estimated at 10 year disease free survival in 13-15%
Vinca alkaloids	1- 75%	5 - 7 days	average 10 months

Table B51 Response outcomes reported in Amgen Romiplostim STA submission to NICE, TA221.

	Response (%)		Time to response	Duration of sustained response
	Splenectomised	Non-Splenectomised		
Cyclosporine	63%	50%	8 weeks	16.2 months
Cyclophosphamide	61%	70%	8 weeks	27 months
Danazol	60%	45%	16 weeks	147.35 months
Dapsone	47%	50%	4 weeks	20.3 months
Mycophenolate mofetil	44%	57%	16 weeks	5.7 months
Anti-D	NA	46%	instant	1 month
IVIg	79%	81%	instant	1 month
Rituximab	58%	58%	8 weeks	18.9 months
Corticosteroids (assuming rescue use)	46%	46%	instant	1 month
Vinca alkaloids	53%	67%	4 weeks	1.4 months

Comparison of eltrombopag response with non-TPO treatments

Eltrombopag is a maintenance treatment. Compared to other maintenance treatments available for cITP the response rate for eltrombopag is high (79% in RAISE). Responses are observed, on average, sooner than in other maintenance

treatment options, at between 15 and 28 days. Interim results from the long term follow up study for eltrombopag, EXTEND, reported responses being maintained over 4 years in some patients whilst remaining on treatment, suggesting a long-lasting treatment benefit.

The maintenance treatments for which the most data was available were rituximab and corticosteroids. Rituximab (total n=463, 14 studies[95;97;98;101;102;104;105;112;113;115;116;121;124;127]) was shown to have an average response rate of 59%, with a time to response of 24.4 days and duration of response of 748.4 days. In corticosteroid studies a response of 54% was reported (total n=135, 5 studies[91;95;110;123;128]) (time to response and duration of response not reported).

Despite their inclusion in the guidelines, the authors acknowledge that the evidence supporting the use of the other treatments was very limited, and in each case the sample size was so small that a high level of uncertainty is associated with all estimates. For dapsone (total n=42, 2 studies[103;107]) the response rate was estimated to be 45% with an average time to response of 35.5 days, the response rate observed in mycophenolate mofetil (total n=55, 3 studies[100;108;117]) was 53% with the duration of response estimated at 50.5 days. For the following treatments it was only possible to determine the response rate: cyclophosphamide (total n=20, 1 study[118]) 85%, danazol (total n=14, 1 study[114]) 36% and vinca alkaloids (total n=12, 1 study[111]) 58%. No relevant evidence for Cyclosporine was indentified.

Compared to treatments typically used as rescue medications in the patient population of interest, such as IVIg and Anti-D, the response rate for eltrombopag appears comparable.

5.8.14 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

No statistical assessment of heterogeneity was conducted. However, it is likely that naïve indirect comparison is confounded by differences in the baseline characteristics of the studies (ITP duration and baseline platelet count were very variable across studies, as was prior treatment history); and by study design and reporting quality: many of the studies listed above would not have been subject to the quality rigour and control applied to the TPO-RA trials conducted for regulatory purposes.

Attempts were made to limit the impact of this heterogeneity by restricting the inclusion of trials to those that most closely match the heavily pre-treated, low platelet count cITP population in RAISE[38;39].

5.8.15 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

Given the limited evidence available, and the questionable quality and relevance of may of the included trials, sensitivity analyses excluding individual trials were not expected to be informative and were not conducted.

5.8.16 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

Not applicable.

5.9 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

5.9.1 If non-RCT evidence is considered (see section 5.2.7), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.6 and 9.7, appendices 6 and 7.

Relevant non-RCTs were retrieved using the same search strategy as outlined in Table B5 for the identification of RCTs.

5.9.2 Relevant eltrombopag non-RCTs

Only one relevant full paper non-RCT pertaining to eltrombopag was identified, in addition, six studies reported in conference abstracts were identified. A number of included studies were related to previously reported RCTs:

- TRA 105325 EXTEND[46] - included patients from:
  - TRA 100773A, TRA 100773B, TRA 102537 RAISE or TRA 108057 REPEAT
- Cooper ASH 2011[53] and Olney ASH 2011[54] re-analysed data from:
  - TRA 100773A, TRA 100773B, TRA 102537 RAISE, TRA 108057 REPEAT or TRA 105387 EXTEND

Details of the included studies are provided in Table B7, Table B52 (methodology), and Table B53 (results).

Table B52 Summary of methodology of relevant non-RCTs for eltrombopag

Trial No	Objectives	Intervention	Participants	Duration	Study Type	Outcome measures
TRA 108057 REPEAT[49]	To evaluate the effect of intermittent eltrombopag dosing	Eltrombopag 50 mg in 3 cycles of repeated intermittent dosing	Subjects with previously treated ITP, who had platelet counts ≥ $20X10^9$/L and ≤ $50X10^9$/L and who had received ≥ 1 prior ITP therapies	3 cycles of an eltrombopag on-therapy period of up to 6 weeks and an off-therapy period of up to 4 weeks	Open-label, single group, repeat dose	• Durability of response; the proportion of subjects who responded to treatment in cycle 2 or 3 (given they responded in cycle 1). Response was defined as a platelet count ≥ $50X10^9$/L and at least 2x baseline • Proportion of subjects achieving a platelet count of ≥$50X10^9$/L and at least 2x baseline • Pharmacodynamic parameters of platelet count (baseline, peak and trough) over 3 cycles • Proportion of subjects requiring rescue treatment • Incidence and severity of bleeding signs and symptoms measured using the WHO Bleeding Scale and the ITP Bleeding Score. • Safety and tolerability
TRA 105325 EXTEND, Saleh and Bussel 2011 ASH, Saleh ASH 2010, Bussel EHA 2010 [44-46;129]	To evaluate the long term effects of eltrombopag	Eltrombopag 50 mg o.d. initial starting dose (dose adjustment algorithm provided in Appendix 6)	Subjects previously enrolled in an ITP study of eltrombopag who completed treatment and follow-up periods (TRA 100773A, TRA 100773B, TRA 102537 RAISE or TRA 108057 REPEAT)	54 months, on-going (Jun 2006 – Feb 2011 data used)	Open-label, single arm, extension	• Safety and tolerability • Proportion of subjects achieving a platelet count ≥$50X10^9$/L during treatment and at least 2x baseline • The proportion of subjects achieving a platelet count ≥ $30X10^9$/L • Maximum duration of platelet count elevation ≥$50X10^9$/L during treatment • Proportion of subjects who responded to eltrombopag in a previous study and who respond to retreatment with a rise in

Trial No	Objectives	Intervention	Participants	Duration	Study Type	Outcome measures
						platelet count to ≥ 50X10^9/L and ≥ 30X10^9/L • The effect of eltrombopag on reduction and/or sparing of concomitant ITP therapies, while maintaining a platelet count ≥50X10^9/L • Proportion of subjects needing rescue treatment (defined as a composite of: new ITP medication, increased dose of a concomitant ITP medication, platelet transfusion, and splenectomy). • Incidence and severity of signs and symptoms associated with ITP measured using the WHO Bleeding Scale • HRQoL (SF36v2, MEI-SF, FACIT-Fatigue and FACT-Th)
Meyer 2011[50]	To assess infection related loss of platelet response during treatment with TPO-RAs	Eltrombopag 25 – 75 mg o.d. Romiplostim 1 – 7 µg/kg weekly	Subjects with chronic ITP who had received ≥1 prior treatment, and had platelet counts <10X10^9/L	NR	Retrospective analysis	• Response to TPO-RA • Transient loss of response • Adverse events
Kuter ASH 2011, part 1 analysis presented (cut off 30 June 2011)	To understand how TPO-RAs impact lives of chronic ITP patients, and the treatment decisions around the use of such agents	Eltrombopag and romiplostim	Patients >18yrs, with chronic ITP and a medical history for at least 12 months who have been treated with a TPO-RA for 4 weeks	Analysis was carried out on 30th June 2011	Observational	• Patient reported outcomes using the SF-36 and the Treatment Satisfaction Questionnaire with Medication (TSQM)
Haselboeck ASH 2011[52]	To assess the function of eltrombopag induced platelets	Eltrombopag and Steroids	NR	Eltrombopag for 3 months	Prospective	• Platelet function assessed by adhesion under high shear conditions, P-selectin expression, and formation of platelet

Trial No	Objectives	Intervention	Participants	Duration	Study Type	Outcome measures
	compared to platelets in patients receiving steroid treatment and no treatment					monocyte aggregates.
Cooper ASH 2011[53]	Assessment of the potential increased risk of cataracts associated with eltrombopag treatment	Eltrombopag regimens according to TRA100773A and B, TRA102537 RAISE, TRA108057 REPEAT and TRA105325 EXTEND	Populations reported in eltrombopag trials	As per trials, EXTEND data from Jun 2006 – Feb 2010, ocular exams up to 6 months post treatment	Retrospective analysis	• Ocular data as reported per trial, including ocular health history and cataract risk factors (chronic corticosteroid use).
Olney ASH 2011[54]	Assessment of the safety and efficacy of eltrombopag in patients ≥65 years	Eltrombopag regimens according to TRA100773A and B, TRA102537 RAISE, TRA108057 REPEAT and TRA105325 EXTEND	Subjects with ITP aged ≥ 65 years in the trials listed in the interventions	As per trials, EXTEND data from Jun 2006 – Feb 2010	Retrospective analysis	• Efficacy and safety in patients ≥65 years

WHO: World Health Organisation; HRQoL: Health Related Quality of Life; FACT-Th/Fatigue scale: Functional Assessment of Cancer Therapy – Thrombocytopenia/fatigue scale; MEI-MF: Motivation and Energy Inventory

Table B53 Results of relevant eltrombopag non-RCTs

Trial No	Patient Characteristics at baseline	Efficacy outcomes	Safety outcomes	Conclusions
TRA 108057 REPEAT[49]	66 patients; median age 50.5 years, 68% female, 71%white/Caucasian/European. 22 patients (33%) receiving other ITP medication, 20 (30%) had a prior splenectomy. 44% had platelet counts between 20–30 $X10^9$/L, 47% > 30–50 $X10^9$/L, 3% > 50 $X10^9$/L.	• 52/65 (80%) evaluable subjects in cycle 1 responded, 45/52 (87%) responded again in cycle 2 or 3 (exact 95% CI: 0.74, 0.94). For cycles 2 and 3, 48 subjects were evaluable who responded in cycle 1; of these 34 (71%) responded in all 3 cycles (exact 95% CI: 0.56, 0.83) • Consistency of response was observed regardless of demographic or baseline disease characteristics • 38/48 (79%) subjects in cycle 1, 35/45 (78%) in cycle 2 and 30/43 (70%) in cycle 3 achieved a platelet count of ≥$50X10^9$/L and at least 2x baseline • No subject received a rescue medication during treatment with eltrombopag or during the off-therapy periods between cycles 1 and 2 or cycles 2 and 3 • A decrease in bleeding (WHO bleeding scale) was observed in each on-therapy period compared to baseline. Bleeding symptoms increased again during off-therapy periods, but generally remained lower than baseline of cycle 1. No WHO bleeding scale grade 3 or 4 bleeds were reported • 8 subjects experienced ≥ 1 haemostatic challenge. Procedures ranged greatly in terms of risk of bleeding. All 8 subjects responded to eltrombopag and none required additional treatment. No abnormal bleeding was reported for any of the procedures	• 68% of subjects reported ≥ 1 on-therapy AE across all cycles and 63% experienced ≥ 1 off-therapy AE • Headache was the most frequently reported AE (21% on-therapy) • Across all 3 on-therapy cycles, 15 subjects (23%) experienced ≥ 1 related AE • No evidence of phototoxicity, cardiotoxicity, renal toxicity, or ocular toxicty	Repetitive administration of eltrombopag produced a consistent and predictable platelet count increase across 3 treatment cycles. No evidence for development of tolerance to eltrombopag was observed; repeated exposure did not diminish response. After cessation of treatment, temporary decreases in platelet count were observed in some subjects, without increases in clinically significant bleeding. Eltrombopag was well-tolerated.
TRA 105325 EXTEND, Saleh and Bussel 2011 ASH (abs no. 3296	At time of data cut off (Feb 2011), 301 subjects had been enrolled, 21% completed, 48% withdrew, and 32%	**Data cut off from Feb 2011 Saleh (n=301)** • Overall, the majority of patients achieved platelet counts ≥ $50X10^9$/L, 88%, at least once • Median platelet count increased to ≥ $50X10^9$/L at week 2 and generally remained ≥ $50X10^9$/L throughout 208 weeks, regardless of splenectomy status or use of concomitant	• AEs and SAEs were observed in 89% and 29% of patients respectively. The most frequent AEs were headache (27%), nasopharyngitis (24%) and upper respiratory tract	Eltrombopag is effective at increasing and maintaining platelet counts of ≥$50X10^9$/L and reducing bleeding symptoms. Eltrombopag has been well

Trial No	Patient Characteristics at baseline	Efficacy outcomes	Safety outcomes	Conclusions
and 3297)[44-46;129]	remain on study. At baseline 38% were splenectomised, 34% were receiving concomitant ITP medication, 53% had received ≥3 prior ITP therapies, platelet counts were ≤15 $X10^9$/L in 43%, >15-<30 $X10^9$/L in 27%, 30-50 $X10^9$/L in 17% and >50 $X10^9$/L in 13% of subjects. As of this report median treatment duration was 121 weeks (range 0.3-237), and 252, 215, 176, 84, and 23 subjects had been treated for ≥6 months, 1, 2, 3 and 4 years respectively.	medications • The incidence of any bleeding symptoms (WHO grade 1-4) reduced from 56% at baseline to 16%, 19% and 9%, and the incidence of clinically significant bleeds (grades 2-4) reduced from 16% as baseline to 3%, 5% and 0% at weeks 52, 104 and 156 respectively. **Data cut off from Feb 2010 (n=299) (Bussel 2011 and Saleh ASH 2010)†** • Median dose 51.5mg/day (range 1-110mg) • Of 299 patients 70% achieved a response ≥50% of the time, and 46% achieved a response ≥75% of the time (response: platelet count of ≥50$X10^9$/L). • Of the 210 patients treated for over 12 months, 79% achieved a response ≥50% of the time, and 56% achieved a response ≥75% of the time • Of the 138 patients treated for over 24 months, 82% achieved a response ≥50% of the time, and 59% achieved a response ≥75% of the time • Reponses were similar regardless of number of prior therapies. • Responses were similar in splenectomised versus. non-splenectomised patients at 65% and 73% respectively	infection (21%). • 13% of patients withdrew because of AEs and 9% because of SAEs • 25 thromboembolic events (TEEs) in 19 (6%) of patients were reported, incidence rate of 3.02/100 patient years (95% CI [1.82-4.71]). Observed TEEs included deep vein thrombosis (10), central nervous system ischemic events (7), myocardial infarction (5) and pulmonary embolism (3). • Hepatobiliary laboratory abnormalities (HBLAs) were reported in 34 (11%) patients, 30 of which were resolved on treatment or after discontinuation. 8 patients withdrew as a result of HBLA. • Independent central review of bone marrow biopsies in >100 patients who had 1-4 years of eltrombopag exposure found no clinically significant increase in reticulin deposition.	tolerated up to 4.5 years, and no new safety indications were observed. This study is on-going.
Meyer 2011[50]	13 patients, 12 eltrombopag and 3 romiplostim (2 patients	• Platelet counts increased in 10 patients treated with eltrombopag and in all patients treated with Romiplostim ~2-4 weeks following onset of treatment.	• Eltrombopag related AEs recognised in 5 patients: arthralgia (3), isolated	Transient loss of response is observed in patients treated with TPO-RAs

Trial No	Patient Characteristics at baseline	Efficacy outcomes	Safety outcomes	Conclusions
	received eltrombopag and romiplostim). Mean age 55 years, 61% female, eltrombopag dose ranged from 25mg twice weekly – 75mg daily, and treatment duration 33-567 days. Historic platelet count <10 $X10^9$/L prior to treatment	• Transient loss of response in 4 of 10 eltrombopag responders and 1 romiplostim responder following infection. Loss of response lasted ~8 days. • 2 of the 4 eltrombopag patients to suffer a transient response suffered a bleeding event, 1 of which required a platelet transfusion. • All patients recovered	elevation of liver enzymes however no further symptoms of hepatitis (2). • Romiplostim related AEs in 2 patients: arthralgia plus pruritus and constipation.	following infections
Kuter ASH 2011, part 1 analysis presented (cut off 30 June 2011)[51]	280 patients, 130 eltrombopag (prior treatments: corticosteroids 44, rituximab 44, romiplostim 42), 150 romiplostim (prior treatments: corticosteroids 58, rituximab 48, eltrombopag 44) baseline characteristic very similar, only differences observed in prevalence of comorbid hyperlipidemia (8% eltrombopag, 16% romiplostim), and incidence of A&E visits prior to switching (16% eltrombopag, 9% romiplostim)	• Median time on treatment 11.6 weeks (4-93) and 10.6 weeks (4-125) for eltrombopag and romiplostim respectively. • Upon enrolment eltrombopag patients reported statistically higher scores on 3 of 8 domains (energy/fatigue, emotional well-being and social functioning), for these three domains differences between treatment cohorts were ±5 points on a 100 point scale. (described as unlikely to be clinically significant) • No difference between the cohorts reported using TSQM. • Compared to the romiplostim treatment cohort, patients in the eltrombopag treatment cohort were more likely to report greater convenience (OR 3.74, p<0.0001), greater overall satisfaction with treatment (OR 1.63, p=0.034), and less fatigue (OR 0.65, p=0.04) subsequent to the switch in their ITP medication.	• NR	No evidence to suggest that patients have significant differences in the odds of achieving greater patient satisfaction, efficacy, or difference in side effects between eltrombopag and romiplostim. Eltrombopag patients reported a greater convenience and overall treatment satisfaction.

Trial No	Patient Characteristics at baseline	Efficacy outcomes	Safety outcomes	Conclusions
Haselboeck ASH 2011[52]	30 patients, 11 eltrombopag (9 female), 13 steroids (5 female), 6 untreated. 26 responders included in comparative analysis (10 eltrombopag and steroids each, 6 untreated)	• Platelet counts were 48.25 $X10^9$/L [45.00-59.00] after eltrombopag-induced platelet rise, 82.75 $X10^9$/L [78.50-112.00] in steroid group and 69.25 $X10^9$/L [65.00-73.00] in untreated group. • Surface coverage under high shear conditions was highest in steroid-treated patients (11.25% [8.10-14.00%]) compared to eltrombopag-treated (5.80% [1.80-9.00%]) and untreated (5.03% [3.80-6.20%]) patients and correlated significantly with the platelet count (r=0.72, p<0.0001) • There were no differences in P-selectin expression [GeoMFI] (1.15 [0.47-2.77] in eltrombopag group, 0.27 [0.10-0.99] in steroid group and 0.59 [0.47-1.44] in untreated group; p=0.34) and platelet monocyte aggregate levels (6.19% [3.91-21.39%] in eltrombopag group, 9.73% [1.88-13.29%] in steriod group, and 6.56% [4.82-8.43%] in untreated group; p=0.93 (between the groups)	• Two patients developed venous thrombosis during eltrombopag treatment	Good functional competence of eltrombopag induced platelets, with no substantial hyperactivity compared to steroid induced platelets.
Cooper ASH 2011[53]	See baseline characteristics of REPEAT and EXTEND reported earlier in table, and of TRA100773A and B and TRA 102537 RAISE reported in Table B10 and Table B11 respectively Total included patients was 392, 14% had pre-existing cataracts or were aphkic/pseudoaphkic, 62% had cataract risk	• NR	• In TRA 100773A and B 4% placebo, and 5% eltrombopag treated patients experienced incident cataract or progression of cataract. All had prior corticosteroid use, and one had increased risk factor at first exam. • In RAISE 10% and 8% of placebo and eltrombopag respectively experienced incident cataract or progression of cataract. All had prior corticosteroid use identified as a risk factor at	A similar proportion of patients in the placebo and eltrombopag treated groups develop cataracts, including in the EXTEND study where eltrombopag exposure could be for >3 years.

Trial No	Patient Characteristics at baseline	Efficacy outcomes	Safety outcomes	Conclusions
	factors (corticosteroid use)		first exam. • In REPEAT no treatment related cataract events • In EXTEND (-Feb 2010, n=299) cataract events in 8% (25), with 24 reporting prior corticosteroid use.	
Olney ASH 2011[54]	See baseline characteristics of REPEAT and EXTEND reported earlier in table, and of TRA100773A and B and TRA 102537 RAISE reported in Table B10 and Table B11 respectively	• Response in ≥65 year olds in: • **TRA100773A:** >50 $X10^9$/L at day 43 - 100% • **TRA 100773B:** >50 $X10^9$/L at day 43 – 74% • **RAISE:** 50-400 $X10^9$/L at any given visit – 42-75% • **REPEAT:** >50 $X10^9$/L&2x baseline in any cycle – 83% • **EXTEND:** 78% responded >50% of the time, and 53% responded >75% of the time.	• Most common AEs, headache, nasopharyngitis, upper respiratory tract infection, diarrhoea • Across all studies: fatigue 11%, arthralgia 10%, constipation 5%, cateracts 4% for 18-49 whilst for >65yr olds it was 19% for each AE • Thromboembolic events in 9% >65 yr olds, versus. 2% and 3% in younger groups. • SAE bleeding events 3% versus. 7% in >65 versus. 18-64 yrs respectively	No significant difference in safety and efficacy between younger and elderly population. Elderly population appears to have more resilient responses and slightly more non-haemorrhagic events.

AE: Adverse event, SAE: Serious Adverse Event; †This abstract was included as it reported additional endpoint data

5.9.1 **Relevant romiplostim non-RCTs**

Two studies were identified; an open label, long-term extension study of Kuter 2008 and earlier romiplostim trials (Bussel 2009, Bussel ASH 2009, Kuter ASH 2010 [61;64;69]), and a prospective, single arm trial (Janssens 2011[62;71]). Methodology of the romiplostim non-RCTs is shown in Table B54. Details of dose adjustment and exposure to study medication are given in Appendix 4. Results are shown in Table B55.

Table B54 Comparative methodology of relevant romiplostim non-RCTs

Trial No	Objectives	Intervention/dose	Participants	Duration	Study Type	Outcome measures
Bussel 2009, Bussel ASH 2009, Kuter ASH 2010 [61;64;69]	To evaluate the long term safety and efficacy of romiplostim	Romiplostim, dose adjustment rules are provided in Appendix 4	≥18 years, ≥1 prior ITP treatments, and had completed the previous Bussel 2006, Kuter 2008 and Newland 2006 studies. Enrolment was allowed once platelet counts were ≤50X109/L and at least 4 weeks had elapsed since participation in previous studies	Enrolment began 2nd August 2004, Bussel 2009 reported cut off in July 2007, Bussel ASH 2009 and Kuter EHA 2010 reported cut off from May 2009, Kuter ASH 2010 reported cut off January 2010	Open-label extension study	• Median platelet response ($50X10^9$/L) • Proportion of patients with a platelet response ≥$50X10^9$/L and at least 2x baseline • Exposure to study medication • Use of rescue medication • Reduction in concomitant ITP medication • Adverse events
Janssens ASH 2011, EHA 2011 [62;71]	To evaluate the safety and efficacy of romiplostim	Romiplostim	≥18 years, ≥1 prior ITP treatments, platelet count ≤30X109/L or uncontrolled bleeding	Median time on treatment 44.29 weeks (maximum 201 weeks)	Prospective, international, single arm study	• Incidence of adverse events and antibody formation • Platelet response defined as either doubling of baseline count and ≥$50X10^9$/L or ≥$20X10^9$/L increase from baseline.

Table B55 Results of relevant romiplostim non-RCTs

Trial No	Patient Characteristics at baseline	Efficacy outcomes	Safety outcomes	Conclusions
Bussel 2009, Bussel ASH 2009, Kuter ASH 2010, (Aug 2004 – Jan 2010 final cut off) [61;64;69]	Patients were eligible if they had completed a previous romiplostim study. After completing previous studies patients were eligible once their platelet counts were ≤50 $X10^9$/L, and at least 4 weeks had elapsed since participation in previous study. N=292, 63% female, median time since diagnosis 4.9 years (range 0.6-46.4), 32.5% splenectomised.	Kuter ASH 2010 (final results): • Median romiplostim exposure 78 weeks (range 1 - 277), median dose 4µg/kg (Q1, Q3 2.2-7.3), after week 12 78% of patients received a dose within 2µg/kg of the patients most frequently administered dose 90% of the time • 94.5% achieved a platelet count of 50 $X10^9$/L during the study, with over 50% achieving this response on ≥90% of visits. After the first week platelets remained within target range of 50-200$X10^9$/L for the median of patients. • 81% (30/37) of patients receiving concomitant ITP medication at baseline were able to discontinue or reduce their dose by ≥25% • Patients were divided into 4 cohorts according to changes in protocol; however median platelet counts were similar between the cohorts and for the overall population[8]	• AEs reported in 98% of participants, • Most common AEs: headache 38%, nasopharyngitis 34%, fatigue 32% • The severity of AEs did not increase with duration on study • AEs did not differ between cohorts[9] • Bone marrow biopsies (carried out on small proportion of patients) showed bone marrow reticulin was present/increased in 11 patients and was generally associated with a longer duration of ITP, splenectomy and higher doses of romiplostim. • 16 patients died, 2 of which were considered as possibly treatment related.	Romiplostim is an important, well tolerated treatment for chronic ITP in adults which rapidly increases and maintains platelet counts.
Janssens ASH 2011, EHA 2011[62;71]	N=407, 60% female, median time since ITP diagnosis 4.25 years (Q1, Q3 1.2-11.4, maximum 57.1), 51%	• Median duration on study treatment 44.29 (Q1, Q3 20.43, 65.86, maximum 201) weeks • No neutralising antibodies were reported.	• All AE's: 377 (93%), SAEs: 122 (30%), Treatment related AE's: 193 (47%), serious, treatment related AEs 29 (7%). • Most common AEs: headache 119	Largest prospective study available for romiplostim safety. In concurrence with previous studies, romiplostim is able to

[9] Cohorts were divided based on the date of study enrolment.
Cohort 1 (Apr 2004 – Feb 2005) Max romiplostim dose 30µg/kg, study entry platelet count ≤50x10^9/L
Cohort 2 (Feb 2005 – May 2006) Max romiplostim dose 15µg/kg, study entry platelet count ≤50x10^9/L
Cohort 3 (May 2006 – Oct 2007) Max romiplostim dose 10µg/kg, study entry platelet count ≤50x10^9/L
Cohort 4 (Oct 2007 – Jan 2010) Max romiplostim dose 10µg/kg, study entry platelet count none.

Trial No	Patient Characteristics at baseline	Efficacy outcomes	Safety outcomes	Conclusions
	splenectomised, 39% receiving concomitant ITP medication		(29%), arthralgia 80 (20%), fatigue 75 (18%), nausea 72 (18%), epistaxis 70 (17%), nasopharyngitis 69 (17%), petechiae 63 (16%) contusion 62 (15%) • 18 patients died, of which 3 were considered treatment related.	safely induce a rapid platelet response in adult ITP patients with low platelet counts or uncontrollable bleeding.

5.9.2 **Critical appraisal of non-RCTs**

The Cochrane Handbook for Systematic Reviews of Interventions states that for non-RCT studies, “there is no single recommended instrument [for assessment of the risk of bias], so review authors are likely to need to include supplementary risk of bias instruments or items”[130]. Different instruments are better suited to different study designs, and therefore it was not possible to use a standardized instrument. Critical appraisals of non-RCTs are largely used to highlight the heterogeneity of studies, it was therefore decided, on balance, not to conduct a formal critical appraisal of the included non-RCT evidence.

5.10 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

5.10.1 **Adverse Events in TRA 100773A[40] and TRA 100773B[42]**

The adverse events reported in TRA 100773A and B are outlined in Table B56. All adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3. Table B57 and Table B58 provide details of adverse events reported in more than 5% of participants in TRA 100773A and TRA 100773B respectively.

During the treatment phase, in TRA 100773A adverse events were similar between the placebo group and all of the eltrombopag dose groups (59% on placebo and 47%- 61% on eltrombopag) [40]. In TRA 100773B a greater proportion of patients receiving eltrombopag compared to placebo experienced an adverse event (59% versus 37%)[42].

Serious adverse events (SAEs) in TRA 100773A were reported with the same frequency in the placebo group and the 50mg eltrombopag group (7%), while no SAEs were reported in the 30 mg and the 75 mg groups[40]. In TRA 100773B, SAEs were reported in 3% and 5% of patients in the eltrombopag and placebo groups respectively[42]. Adverse events considered by the investigators as related to study medication were higher in the 75 mg group (36%) than in placebo group (31%) in TRA 100773A[40]; in TRA 100773B a higher proportion was reported in the eltrombopag group compared to placebo (26% versus 11%)[42].

The most common adverse event reported in each trial was headache, with a similar proportion of reports in the placebo and eltrombopag groups. In TRA 100773A 17% of patients on placebo reported fatigue, compared to between 3% and 7% in the eltrombopag groups[40]. There was no significant difference observed between eltrombopag and placebo in any individual adverse event in either of the trials.

Table B56 Overall summary of adverse events in TRA 100773A[40] and TRA 100773B[42]

Trial No.	TRA 100773A[40]				TRA 100773B[42]	
AEs during entire study by subject, n (%)	Placebo N = 29	Eltrombopag 30 mg N = 30	Eltrombopag 50 mg N = 30	Eltrombopag 75 mg N = 28	Placebo N = 38	Eltrombopag N = 76
Any AE	17 (59)	14 (47)	14 (47)	17 (61)	14 (37)	45 (59)
Any SAE	2 (7)	0 (0)	2 (7)	0 (0)	2 (5)	2 (3)
AEs related to study medication	9 (31)	9 (30)	8 (27)	10 (36)	4 (11)	20 (26)
AEs leading to withdrawal	2 (7)	0	2 (7)	1 (4)	2 (5)	3 (4)

AE: Adverse Event, SAE: Serious Adverse Event

Table B57 Adverse events in 5% or more patients in any treatment group in TRA 100773A[40]

Event, n (%)		Eltrombopag		
	Placebo N = 29	30 mg N = 30	50 mg N = 30	75 mg N = 28
Any AE	17 (59%)	14 (47%)	14 (47%)	17 (61%)
Headache	6 (21)	4 (13)	3 (10)	6 (21)
Fatigue	5 (17)	0	1 (3)	2 (7)
Constipation	2 (7)	1 (3)	0	2 (7)
Rash	1 (3)	1 (3)	0	2 (7)
AST increased	0	1 (3)	0	2 (7)
Anaemia	2 (7)	1 (3)	1 (3)	1 (4)
Peripheral oedema	2 (7)	0	1 (3)	1 (4)
Diarrhoea	2 (7)	0	0	1 (4)
Taste disturbance	2 (7)	0	0	1 (4)
Epistaxis	0	4 (13)	0	0
Pain in extremity	1 (3)	2 (7)	0	0
Arthralgia	3 (10)	1 (3)	0	0
Abdominal distension	2 (7)	1 (3)	0	0
Haemorrhoids	2 (7)	0	0	0

AE: Adverse Event

Table B58 Adverse events in 5% or more patients in any treatment group in TRA 100773B[42]

Event, n (%)	Placebo N = 38	Eltrombopag N = 76
Any AE	14 (37)	45 (59)
Headache	4 (11)	6 (8)
Nasopharyngitis	3 (8)	5 (7)
Nausea	0	6 (8)
Diarrhoea	1 (3)	4 (5)
Vomiting	0	4 (5)
Gingival bleeding	3 (8)	0

AE: Adverse Event, SAE: Serious Adverse Event

5.10.2 **Adverse events in TRA 102537 RAISE[38;39]**

An overall summary of the adverse events reported in RAISE is provided in Table B59. The proportion of patients experiencing AEs and SAEs was similar between the placebo and eltrombopag groups, with the placebo group showing higher figures in both instances (AEs: 92% and 87%; SAEs: 18% and 11%). The proportion of adverse events considered by the investigators treatment related was higher in the eltrombopag group (36% versus 30%).

Table B59 Overall summary of adverse events in TRA 102537 RAISE[38;39]

	Placebo N = 61		Eltrombopag N = 135	
AEs during treatment phase, n (%)	**Number of subjects**	**Number of events**	**Number of subjects**	**Number of events**
Any AE	56 (92)	411	118 (87)	749
Any SAE	11 (18)	17	15 (11)	21
AEs related to study medication	18 (30)	48	48 (36)	158
AEs leading to withdrawal	4 (7)	6	12 (9)	15

AE: Adverse Event, SAE: Serious Adverse Event

Table B60 provides details of all adverse events experienced by at least 5% of patients in either treatment group in RAISE. As with TRA 100773A and B the most common adverse event was headache, similarly reported in the placebo and eltrombopag groups (33% versus 30% respectively)[38;39].

Table B60 Adverse events in 5% or more patients in either group, TRA 102537 RAISE[38;39]

Event , n (%)	Placebo N=61	Eltrombopag N=135
Subjects with Any AE	56 (92)	118 (87)
Headache	20 (33)	41 (30)
Diarrhoea	6 (10)	17 (13)
Nausea	4 (7)	16 (12)
Nasopharyngitis	8 (13)	14 (10)
Upper respiratory tract infection	7 (11)	14 (10)
Fatigue	8 (13)	13 (10)
Pain in extremity	6 (10)	9 (7)
ALT increased	4 (7)	10 (7)
Vomiting	1 (2)	10 (7)
Urinary tract infection	4 (7)	9 (7)
Arthralgia	3 (5)	9 (7)
Pharyngolaryngeal pain	3 (5)	9 (7)
Myalgia	2 (3)	8 (6)
Pharyngitis	1 (2)	8 (6)
AST increased	2 (3)	7 (5)
Epistaxis	6 (10)	7 (5)
Back pain	3 (5)	7 (5)
Influenza	3 (5)	7 (5)
Cough	4 (7)	6 (4)
Abdominal pain upper	5 (8)	6 (4)
Constipation	5 (8)	6 (4)
Dizziness	6 (10)	5 (4)
Pruritus	5 (8)	4 (3)
Cataract	4 (7)	4 (3)
Hypertension	3 (5)	4 (3)
Oedema peripheral	6 (10)	2 (1)
Dyspepsia	4 (7)	2 (1)
Ecchymosis	4 (7)	2 (1)
Insomnia	4 (7)	2 (1)
Anxiety	3 (5)	2 (1)
Conjunctival hemorrhage	3 (5)	2 (1)
Contusion	3 (5)	2 (1)
Neck pain	3 (5)	2 (1)
Non-cardiac chest pain	3 (5)	2 (1)
Abdominal distension	3 (5)	1 (<1)
Conjunctivitis	4 (7)	1 (<1)
Fall	3 (5)	1 (<1)
Swelling face	3 (5)	1 (<1)
Cellulitis	4 (7)	0
Eye swelling	3 (5)	0

AE: Adverse Event

Table B61 provides details of adverse events of special interest. Notably, the incidence of bleeding events both on- and post-treatment was higher in the placebo group. The

incidence of on-treatment bleeding SAEs was significantly higher in the placebo versus eltrombopag group (p=0.033, 2-sided) .

Table B61 Adverse events of special interest in TRA 102537 RAISE[38;39]

	Treatment Group, n (%)	
	Placebo N=61	Eltrombopag N=135
Bleeding AE*		
On-treatment bleeding event	19 (31)	26 (19)
On-treatment serious bleeding event‡	4 (7)	1 (<1)
Post-treatment bleeding event	6 (10)	6 (4)
Post-treatment serious bleeding event§	1 (2)	2 (1)
Thromboembolic event	0	3 (2)
ALT ≥3x the upper limit of normal	2 (3)	9 (7)
Total Bilirubin >1.5x upper limit of normal	0	5 (4)
Cataract¶**	6 (10)	11 (8)
Malignant disease‖	1 (2)	1 (<1)
Hyperglycaemia ≥7.22 mmol/L**††	30 (50)	42 (31)
Reoccurrence of thrombocytopenia‡‡	4 (7)	9 (7)

ALT=alanine aminotransferase. *Severity of adverse events, including bleeding adverse events, was reported according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0. ‡Significantly lower for eltrombopag versus placebo on the basis of a two-sided Fisher's exact test (p=0・03). §Bleeding reported for one patient in each treatment group more than 30 days after study discontinuation; the remaining patient had a bleeding event while undergoing abdominal surgery for rectosigmoid cancer without prophylactic anticoagulant treatment. ¶Based on ocular examination; incident cataract (eltrombopag, n=7; placebo, n=3); cataract progression (eltrombopag, n=4; placebo, n=3). ‖Malignant diseases were rectosigmoid cancer in one patient on day 92 of eltrombopag treatment and transformation of myelodysplastic syndrome to acute myeloid leukaemia in one patient 173 days after discontinuation of placebo. **Events typically associated with corticosteroid use. ††Significantly lower for eltrombopag than for placebo on the basis of a logistic regression analysis adjusted for baseline glucose above threshold and for baseline diabetes (OR 0・417, 95% CI 0・207–0・841; p=0・02). ‡‡Defined as patients with platelet counts lower than 10 000 per μL and at least 10 000 per μL lower than baseline during the first 4 weeks of interruption (>1 day) or discontinuation of study treatment

A post hoc analysis of patients treated with concomitant medications showed a stastically significant reduction of steroid related side effects, including dyspepsia, peripheral oedema and hyperglycaemia in patients treated with eltrombopag.

5.10.3 **Non-RCT safety data**

5.10.4 Cooper ASH 2011[53] and Olney ASH 2011[54]

Both the Cooper and Olney ASH 2011 abstracts provide further analysis of the five eltrombopag trials TRA 100773A, TRA 100773B, TRA 102537 RAISE, TRA 108057 REPEAT, and TRA 105325 EXTEND. The Cooper ASH 2011 study looked at risk of cataract[53] and Olney ASH 2011 looked at the efficacy and safety of eltrombopag in patients >65 years old[54]. Cooper's analysis of ocular data stems from observations during pre-clinical trials which saw an increased incidence of cataract in rodent populations, although not in canine populations. Both of these subgroup analyses found no statistically significant difference in the reported outcomes between the groups.

5.10.5 Give a brief overview of the safety of the technology in relation to the decision problem.

Adverse events of special interest identified by the RCTs included hepatobiliary, thromboembolic, ocular related and bleeding related events. The RCTs indicate that eltrombopag was well-tolerated and the incidence and severity of adverse events were similar in the placebo and eltrombopag groups, with the exception of bleeding AEs which were significantly lower in patients treated with eltrombopag. In addition, RAISE found that a reduction in side effects commonly associated with corticosteroids was achieved in subjects treated with eltrombopag compared with placebo.

5.11 Interpretation of clinical evidence

5.11.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Eltrombopag is one of two licensed drugs in a new class of treatments for cITP, the TPO-RAs, which work by activating the TPO receptor and thereby stimulating platelet production. The pivotal trials for eltrombopag and romiplostim, showed that both compounds are highly effective when compared to their respective placebo control arms.

Comparisons of the relative efficacy of eltrombopag, romiplostim and non-TPO treatments provided in sections 5.2 to 5.5, 5.7 and 5.8 are summarised below.

Efficacy of eltrombopag

Eltrombopag, has been shown through three randomised, double-blind placebo controlled trials (TRA 10773A, 10773B and RAISE) to be an effective, well-tolerated treatement for patients with relapsed/refractory cITP.

The SPC indication for Eltrombopag is stated as:

> "Revolade [eltrombopag] is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Revolade may be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated".[3]

The randomised, double-blind RAISE trial compared eltrombopag in addition to standard of care with placebo in addition to standard of care over a six-month period in adult patients, diagnosed with primary ITP for longer than six months, with platelet counts ≤ $30x10^9$/L, and who had responded to one or more previous ITP treatments. The trial enrolled 197 patients.

The patients in RAISE represent a patient population with cITP and low platelet counts who are heavily pre-treated and refractory. In both the placebo and treatment arms the median platelet count at baseline was $16x10^9$/L (range 8 to $22x10^9$/L). In the placebo and eltrombopag arms, respectively, 52% and 56% of patients had received ≥3 prior ITP treatments, and 18% and 26% had received five or more[38;39]. Over 20% of all the patients reported clinically significant bleeding (WHO grade 2-4) at baseline[38;39].

The primary outcome was the odds of achieving a response (50-$400x10^9$/L) at any point during the six month treatment period for eltrombopag compared with placebo; this primary endpoint was met, with OR= 8.2; p<0.0001. In the eltrombopag arm the median platelet count remained between 53.0 and $73.5x10^9$/L from day 15 onwards, indicating that patients

responded rapidly to treatment and maintained this response. Furthermore, it allowed them to reduce the use of concomitant and rescue ITP medications[38;39].

Eltrombopag effectively reduced bleeding symptoms during the trial[38;39].The odds ratio for experiencing any bleeding event (WHO grade 1-4) was 0.24 in patients receiving eltrombopag versus placebo ($p<0.001$). The odds ratio for experiencing a clinically significant bleed (WHO grade 2-4) was 0.35 in patients receiving eltrombopag versus placebo ($p<0.001$). The odds ratio of suffering a clinically significantly bleeding event (CTCAE grade ≥3) was 0.32 in patients treated with eltrombopag compared with placebo[73].

Overall, Grade 3-4 adverse events were observed in only 11% and 15% of the placebo and eltrombopag arms respectively, and serious adverse events were more common in the placebo group.

The EXTEND long term extension study, still ongoing, recruited patients from RAISE and other eltrombopag cITP trials, evaluating the safety and efficacy of eltrombopag for over four years.[44-46;129] Long term safety and efficacy data from EXTEND indicate that eltrombopag is well tolerated and effective at increasing and maintaining platelet counts ≥$50x10^9$/L, reducing the use of concomitant ITP medications and reducing bleeding symptoms, with exposures of up to 4.5 years [46]. Patients have been treated with eltrombopag for a median of 121 weeks. Responses (≥$50x10^9$/L) were observed in 88% of patients at least once, and clinically significant bleeds (WHO 2-4) were reduced from 16% at baseline to 0% at 156 weeks. Serious adverse events were experienced by 29% of patients, and the withdrawal rate due to adverse events was 13%[46].

In summary:

RAISE showed eltrombopag to be well tolerated and highly effective in raising platelet counts to safe levels and in reducing bleeds[38;39] compared to placebo. This trial confirmed the evidence from two 6-week trials (TRA 100773A and TRA 100773B[40;42]) showing eltrombopag's ability to increase platelet counts to a safe level. A long term extension study, EXTEND, confirms that the benefits of eltrombopag can be maintained over the long term[44-46;129].

Comparative efficacy of eltrombopag and romiplostim

There are no head-to-head comparisons of eltrombopag and romiplostim. However, Kuter 2008[60;131] reports the results of two pooled RCTs (one in splenectomised and one in non-splenectomised patients) studying romiplostim and placebo in a comparable patient population to that in RAISE.

While there are some differences in the baseline characteristics of RAISE and Kuter 2008, the inclusion criteria clearly indicate that the trials were designed to include a broadly similar, relapsed/refractory cITP population. Given the heterogeneity of cITP, the limited sample size of these studies and the fact that to be able to recruit enough patients, the studies had to be conducted in diverse geographical locations with different standards of care, differences between the populations are to be expected. A higher proportion of splenectomised patients, a longer overall diagnosis of ITP and a higher number of prior ITP therapies used before enrolment were observed in Kuter 2008[60;131] compared to a higher proportion of baseline concomitant medication use in RAISE. These differences appear to be primarily driven by the study design of Kuter 2008 which, by pooling the results of two studies, ensured a 50:50 split of splenectomised versus non-splenectomised patients.

RAISE[38;39] had 36% splenectomised patients. Patients who had undergone splenectomy had a longer duration of ITP and received more prior ITP medications than non-splenectomised patients. When the population of RAISE is analysed according to splenectomy status the differences between the trials become less pronounced. Of note, RAISE had numerically more splenectomised patients than Kuter 2008.

Kuter 2008[60;131] reported a higher prior use of IVIg and Anti-D than RAISE[38;39]. Baseline concomitant therapy use is lower in Kuter 2008 than in RAISE. Kuter 2008 was run only in the USA and Western Europe, whereas RAISE included a wider range of countries (See Table B8). Differences in treatment practice are likely to reflect resource constraints and standard of care in some countries in which RAISE was run, as well as reflecting the individualised nature of therapy.

Patients in the control arm of RAISE experienced a lower rate of grade 2 or higher bleeds compared to the control arm of Kuter 2008 (see Table B38). The same difference is observed in grade 3 or higher bleeds in splenectomised patients. This may be attributable to the higher rate of baseline concomitant medication use in RAISE. However, it is worth noting that the FDA Advisory Committee Briefing Document[65] highlights that differences were observed within the Kuter 2008 trial itself, noting that "ITP patients in the AMG 531 (romiplostim) group may be less refractory to current first-line ITP therapies; a significant fraction of patients (17%) in the AMG 531 group arm had recent splenectomy (< 6 months) versus none in the placebo arm. In comparison with the placebo group, the AMG 531 group may consist of patients with potentially less refractory disase. Prior bleeding and prior ITP medication histories are consistent with this interpretation regarding splenectomy. These considerations (which suggest less refractory disease in the AMG 531 group as compared with the placebo group) should be kept in mind in interpreting the results of the pivotal studies."

On balance it was considered appropriate to compare the two trials. Adjusted indirect comparisons of four endpoints were carried out in three groups of patients; overall response, durable response, CTCAE bleeding grades 2-5 and grade 3-5 were investigated in the overall population and in splenectomised and non-splenectomised patients.

The trials were designed differently and used different endpoints, so to facilitate an indirect comparison of durable and overall response, the post hoc analysis of the RAISE data was used.

The following considerations need to be kept in mind as differences in the trial designs may bias the comparison of the post-hoc RAISE analysis with the Kuter 2008 analysis: (See section 5.7.7 for further detail)

These include:

- Timing of platelet count assessments
- Different timeframes in which patients were allowed to reduce concomitant ITP medications
- Differences in response definitions ie ($50\text{-}400 \times 10^9$/L in RAISE and $\geq 50 \times 10^9$/L in Kuter 2008).
- Differences in definitions of "period of rescue medication" and "transient response" in the post-hoc RAISE analysis compared to Kuter 2008.

The indirect comparisons estimated an odds ratio for durable response of 0.32 (95% CI 0.03 to 3.14) and for overall response of 0.22 (95% CI 0.05 to 1.02) for eltrombopag versus. romiplostim[73]. These point estimates are not statistically significant, as the 95% confidence intervals cross 1.0 (which suggests no evidence of a difference in efficacy).

The indirect comparison of bleed rates was based on the assumption that Kuter 2008 used a scale equivalent to the CTCAE scale to report adverse events. Although the scale used appeared analogous to CTCAE according to the description provided, this is not confirmed[60;131]. The relative risk of Grade 2-5 bleeding events was 0.74 (95% CI 0.26 to 2.10) and Grade 3-5 bleeding events 1.70 (95% CI 0.27 to 10.81) for romiplostim versus. eltrombopag[73]. Again, the point estimates were not statistically significant.

The indirect comparison found no statistical difference between the relative efficacy of eltrombopag and romiplostim; efficacy of the drugs was therefore assumed to be the same. The confidence intervals around the estimated treatment effects are wide, and the point estimates favoured romiplostim for the platelet response endpoints and both treatments (depending on endpoint and subgroup) for the bleed endpoints. In addition a number of potential biases may be affecting the indirect comparison. These are discussed in Section 5.7.6. In an orphan disease area where treatment practice is variable, the uncertainty is not unexpected. We estimate that 2,873 patients would be required for an equivalence RCT of eltrombopag versus romiplostim with platelet response as the primary endpoint and a tolerance limit of 5%, while 2,273 patients would be required to demonstrate non-inferiority. Implementation of a clinical trial of this magnitude is not feasible in an orphan disease, and even if it were possible, data would not be available within a meaningful timeframe.

The lack of evidence to support any differences in efficacy or safety between romiplostim and eltrombopag is reflected in the two recently issued independent clinical guidelines developed by expert panels and international working groups, which do not favour one drug over the other and recommend the drugs as a class. The International Consensus Report guidelines present the results of eltrombopag and romiplostim together, and state that, “Data from phase 1-3 trials have demonstrated that both drugs are highly effective in increasing the platelet count in both healthy volunteers and ITP patients”[7]. The ASH guidelines recommend “Thrombopoietin receptor agonists for patients at risk of bleeding who relapse after splenectomy or who are contraindicated to splenectomy and who have failed at least one other therapy”[10], with no preference for either drug given.

In summary

Given the level of uncertainty and potential biases, and the fact that clinical guidance recommends the TPO-RAs as a class, the base case analysis for the cost-effectiveness model assumes that the treatments offer equal efficacy.

Comparative efficacy of eltrombopag and non-TPO treatments

Summaries of the efficacy of each comparator were performed using a naïve indirect comparison approach. Methods and findings are described in Section 5.8.

The maintenance treatments for which the most data was available were rituximab and corticosteroids. Rituximab (total n=463, 14 studies[95;97;98;101;102;104;105;112;113;115;116;121;124;127]) was shown to have an average response rate of 59%, with a time to response of 24.4 days and duration of response of 748.4 days. In corticosteroid studies a response of 54% was

reported (total n=135, 5 studies[91;95;110;123;128]) (time to response and duration of response not reported).

Despite their inclusion in the guidelines, evidence supporting the use of the other treatments was very limited, and in each case the sample size was so small that a high level of uncertainty is associated with all estimates. For dapsone (total n=42, 2 studies[103;107]) the response rate was estimated to be 45% with an average time to response of 35.5 days, the response rate observed in mycophenolate mofetil (total n=55, 3 studies[100;108;117]) was 53% with the duration of response estimated at 50.5 days. For the following treatments it was only possible to determine the response rate: cyclophosphamide (total n=20, 1 study[118]) 85%, danazol (total n=14, 1 study[114]) 36% and vinca alkaloids (total n=12, 1 study[111]) 58%. No comparable populations for cyclosporine were identified, and responses in rescue treatments were as expected (high response rates, short times to response and short response durations).

In summary

The International Consensus Report on ITP shows that there are numerous second line treatment options for ITP[7], but the evidence supporting their use is very limited and many of these are unlicensed for use in ITP, with few randomised studies available, particularly for a refractory population similar to that described in RAISE. It is worth nothing that these options can be limited by their tolerability profiles and/or loss of response. The international guidelines state that the TPO-RA class are the only class of drugs with RCT evidence to demonstrate efficacy and safety in these patients and give them a Grade A recommendation.

5.11.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

RAISE is the largest randomised, placebo controlled study conducted in chronic ITP, and is methodologically strong. Following a critical appraisal carried out according to the Cochrane guidelines, the study was associated with a limited risk of bias. Its findings are supported by the results of EXTEND, which show that eltrombopag can maintain its efficacy and is tolerated for up to 5 years (longest current follow-up). The average drug dose over the extension period remained close to the initial starting dose of 50mg, at 51.5mg[45].

The evidence supporting eltrombopag lacks data directly comparing eltrombopag to other non-rescue treatments. The adjusted indirect comparison performed to compare eltrombopag with romiplostim was associated with a number of potential biases, including: the imputation of data required in the post hoc analysis of durable response for RAISE, imbalances between the severity of patients in the romiplostim and placebo arms of Kuter 2008 and differences in trial protocols regarding concomitant therapy reduction and definition of endpoints. For the non-TPO comparators a lack of relevant RCT evidence necessitated performance of a naïve indirect comparison in order to assess relative efficacy. This comparison is associated with a high level of uncertainty due to the heterogeneity of the studies compared and their quality, a limitation in the evidence base that was highlighted in TA221[33].

5.11.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

There is a lack of robust evidence supporting the traditional maintenance treatments for patients with refractory cITP. In contrast, the clinical benefits of the TPO-RAs have been shown in well designed randomised controlled trials. The RAISE trial assessed both platelet response and bleeding rates as efficacy outcomes: these are objective measures that are directly relevant to the clinical benefit obtained by patients. The odds of experiencing clinically significant bleeding (WHO scale 2-4) were reduced by two-thirds in patients treated with eltrombopag relative to placebo (OR 0.35, $p<0.001$).

The platelet threshold of $50x10^9$/L is thought to constitute a suitable definition of response in clinical trials, although many haematologists in clinical practice would set target platelets counts between 30 and 50 $x10^9$/L unless the patients were in need of an invasive procedure or facing other circumstances (eg. Lifestyle) requiring a higher platelet threshold. The platelet threshold acts as a surrogate for the risk of bleeding.

The evidence supporting eltrombopag lacks data directly comparing eltrombopag to other non-rescue treatments. Systematic reviews were carried out to identify studies reporting relevant comparator treatments, and indirect treatment comparisons were conducted where possible and appropriate.

The evidence base for non-TPO-RA treatments consists of small, non-randomised and relatively old studies.

5.11.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

The current treatment guidelines for ITP state that treatment is rarely recommended for patients with platelet count greater than $50x10^9$/L unless clearly identified bleeding risks are present. The main aim is to achieve a haemostatic platelet count for the individual[7]. The study design of RAISE reflects these recommendations, with responses registered if platelet counts rise above $50x10^9$/L but the eligibility thresehold set at $30x10^9$/L where there is dire risk of bleeding.[38;39]

The current SPC for eltrombopag is largely based on clinical evidence taken from RAISE, therefore the recommended starting dose of 50mg and individual dose adjustments are mostly based on the clinical trial.

Eltrombopag is indicated for “adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) in splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)” and “may be considered as second line treatment for adult non-

splenectomised patients where surgery is contraindicated" (SPC licence).[3] Reasons for not having had a splenectomy were not recorded in RAISE. Clinically, there is no reason to believe that the contraindicated subgroup would be treated differently or would experience different outcomes to those in the overall non-splenectomised population. The inclusion criteria and baseline characteristics seen in RAISE indicate that the population is chronic and relapsed/refractory, with median platelet count of $16x10^9$/L, over half having received more than three prior ITP treatments and 36% having undergone splenectomy.[38;39]

Treatment of cITP in the UK is usually only initiated when patients are symptomatic and/or at risk of bleeding. Patients included in RAISE are likely to reflect patients who would be treated in the UK: over 70% of patients in RAISE reported bleeding symptoms at baseline. RAISE is an international trial conducted in countries with varying levels of healthcare expenditure, and this is evident in some of the baseline patient characteristics, e.g. lower use of rescue medication compared to countries with higher healthcare expenditure (Appendix 15). Despite these differences in treatment algorithms, it is assumed that the relative efficacy reported in RAISE is likely to be relevant to the UK population.

From June 2008 to January 2010, prior to the eltrombopag licence being issued, GSK initiated a named patient programme in the UK. Patients with cITP and platelet counts $<30x10^9$/L were eligible to receive eltrombopag. Ultimately fourteen patients received eltrombopag under this programme, with clinical data available for ten cases. 90% of the patients had received ≥4 previous therapies for cITP. Patients had received a number of different treatments, broadly reflective of those described in treatment guidelines. There was a history of bleeding symptoms in 75% of cases. In this highly refractory population, fifty percent of cases responded to therapy and attained normal platelet counts $>150x10^9$/L which were maintained throughout the period of treatment with eltrombopag. One further case had an initial response but despite continued therapy became thrombocytopenic.

Adverse events included failure to achieve similar initial response to eltrombopag following a break in therapy, sudden thrombocytopenia, blurred vision, nausea, diarrhoea, arthralgia and non-haemorrhagic, non-petechiael rash.

The fact that clinicians approached GSK asking for patients to be included in the named programme highlights the fact that there is a population of patients within the UK who have received a number of treatments for their cITP yet still have significant unmet need.These patients are likely to be characteristic of a *proportion* of the population *within* RAISE who exhibit more severe characteristics of cITP.

Eltrombopag has been shown to be an effective treatment for cITP and no significant differences in terms of efficacy and safety have been found between eltrombopag and romiplostim. Market research indicates that both physicians and patients would appreciate a choice of TPO-RA treatments, with an equal preference for romiplostim and eltrombopag demonstrated[37]. The availability of eltrombopag would provide patients and clinicians with a choice of an oral therapy as an alternative to subcutaneous injections, which may be inconvenient for many patients.

6 Cost effectiveness

Key messages

- A Markov model was developed that was structurally representative of the treatment of cITP.
- A pathway incorporating eltrombopag was compared to a pathway without TPO-RAs (non TPO-RA pathway) and a pathway incorporating romiplostim – the current standard of care.
- The base case uses an appropriate set of assumptions, including some from the appraisal of romiplostim (TA221) to relate short term trial data to long term costs and outcomes.
- Eltrombopag is cost-effective versus a non TPO-RA pathway and romiplostim in both splenectomised and non splenectomised patients in the base case.
- Romiplostim is not cost-effective versus a non TPO-RA pathway in the base case. However a sensitivity analysis demonstrates that romiplostim can be considered cost-effective under plausable assumptions.
- An alternative evaluation was conducted that used alternative data from the eltrombopag clinical trial program and an updated systematic review. In this evaluation neither TPO-RA is cost-effective versus a non TPO-RA pathway.
- A key driver of the cost-effectiveness of TPO-RAs versus a non TPO-RA pathway is the assumed rate at which patients receive rescue medication. The true rate is uncertain but the costs of expensive rescue medications, namely IVIg, have been found to account for a large proportion of total management costs for cITP patients in the UK. The severe, refractory population addressed in this decision problem are likely to require frequent rescue treatment.
- Assuming no difference in efficacy between the TPO-RAs, eltrombopag is significantly less costly and is therefore cost effective versus romiplostim in both patient groups. This is driven by the relative costs of TPO-RAs.
- A sensitivity analysis incorporating relative efficacy estimates, based on the point estimates of an indirect comparison for overall response, does not change the interpretation of the base case results. Incremental analysis demonstrates that although accruing slightly fewer QALYs, eltrombopag is still significantly less costly than romiplostim and is the preferred treatment option at a willingness to pay threshold of £20,000/QALY. The QALY difference in this analysis is not considered clinically meaningful for the following reasons: the results of the indirect comparison were not significant, there is inherent uncertainty in such a comparison compounded here by small patient numbers (orphan disease) and the heterogenous nature of cITP, and the clinical community view the TPO-RAs as interchangeable.
- The comparative evidence base for TPO-RAs is uncertain. This is unlikely to improve as the sample size required to prove non-inferiority would require over 2000 cITP patients. This is not likely to be feasible in an orphan disease such as cITP.
- Eltrombopag provides patients and clinicians with the choice of a cheaper, oral alternative in a class of effective drugs that increase platelet counts and reduce a patient's risk of bleeding.

6.1 Published cost-effectiveness evaluations

Identification of studies

6.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 9.10, appendix 10.

A systematic search of the cost-effectiveness literature was carried out on the 6th February 2012 in the following databases: Embase, Medline and Medline-in-process, Econlit, HEED and NHS EED.

Full details of the search strategies are included in appendix 10.

Search strategies included controlled vocabulary terms applicable to the particular database. Free-text terms were used in all searches. The controlled vocabulary used was MeSH terms in Medline, Medline in process and NHS EED; Emtree terms in Embase. The search strategies in Econlit and HEED included terms for ITP only as these databases index economic literature only. The search strategies in Medline, Medline in process, Embase and NHS EED included terms for ITP and a filter to identify cost studies. All searches were limited to 2009 and onwards to update the systematic review in the previous eltrombopag submission which did not identify any cost-effectiveness studies published prior to 2009.

The inclusion criteria were as follows:

- Target population: Adults (≥18 years) with ITP as a primary diagnosis with median/mean platelet counts < 30 $x10^9$/L at baseline. Studies where some patients had a platelet count > 30 $x10^9$/L at baseline were also included in the review, providing some patients in the study had a platelet count <30 $x10^9$/L.
- Types of study: Cost-effectiveness studies and cost-utility analyses.

The exclusion criteria were as follows:

- Studies not in the English language.
- References to studies reported as conference abstracts.

No cost-effectiveness studies were identified by the systematic review. Details of abstracts reviewed and studies excluded at each stage of this update review are presented in the PRISMA flow diagram in Figure B16.

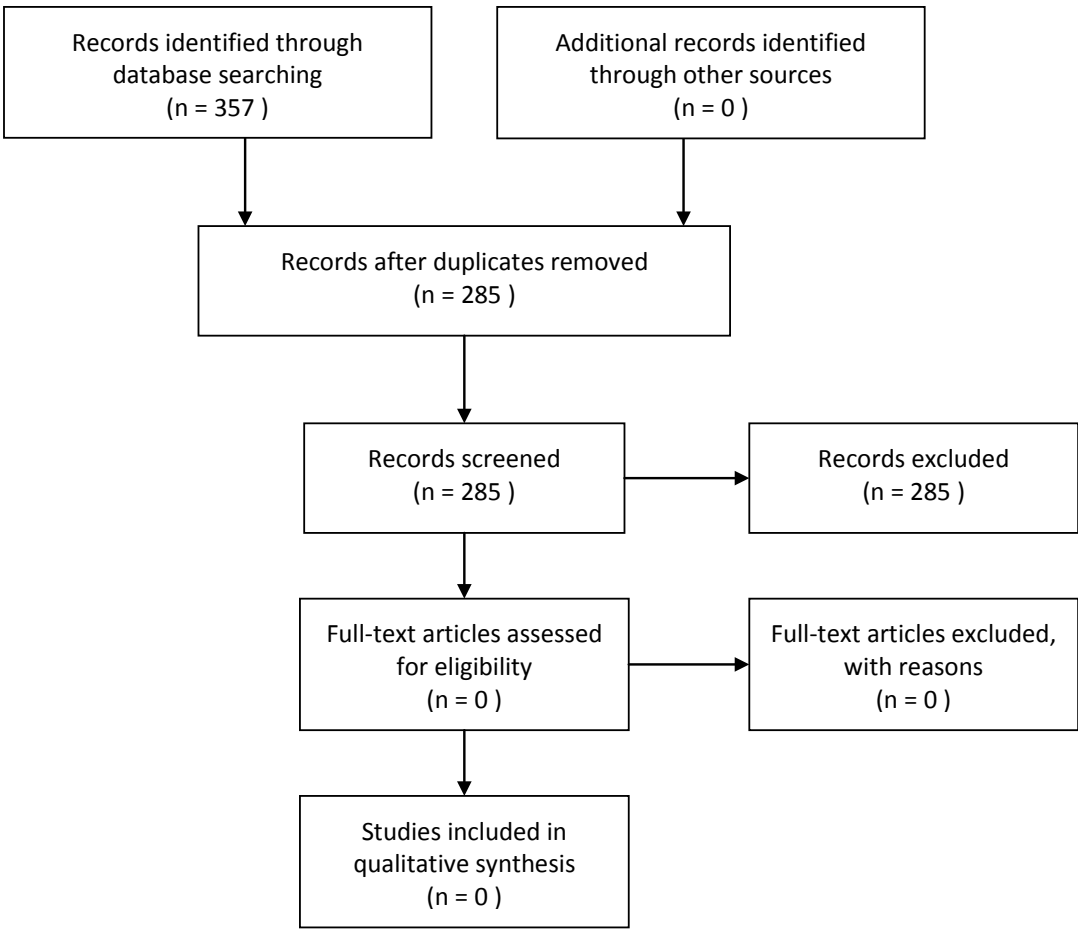


Figure B16: PRISMA diagram for systematic review of cost-effectiveness studies

Description of identified studies

The modelling approach taken in the NICE technology appraisal of romiplostim is discussed in some detail throughout this submission. This has been described in a publication of the STA.[75;132] The initial submission to NICE of eltrombopag has also been published[133;134] and is not discussed in detail in this submission.

Description of identified studies

6.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

N/A

6.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[10] or Philips et al. (2004)[11]. For a suggested format based on Drummond and Jefferson (1996), please see section 9.11, appendix 11.

N/A

6.2 De novo analysis

Patients

6.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.4 and 5.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

This de novo economic evaluation was designed to assess the cost-effectiveness of treatment with eltrombopag in two patient populations:

- Adult splenectomised cITP patients who are refractory to other treatments (e.g. corticosteroids, IVIg).
- Adult non-splenectomised cITP patients who are contraindicated to surgery and who are refractory to other treatments (corticosteroids, IVIg).

These patient groups are consistent with the licence for eltrombopag and with the patients who were included in the RAISE trial. Patients entering the pivotal trial are considered to be a severe, refractory cITP population as discussed in detail in section 5.3.4.

On entering RAISE, approximately one third of patients were splenectomised. Reasons for not having had a splenectomy weren't recorded and in the economic model these patients were assumed to be representative of patients for whom splenectomy is contraindicated. Clinically there is no reason to believe that the contraindicated subgroup would be treated differently or would experience different outcomes to those in the overall non-splenectomised population.

Model structure

6.2.2 Please provide a diagrammatical representation of the model you have chosen.

The model is a state transition Excel-based Markov cohort model in which patients cycle through a defined sequence of treatments.

[10] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

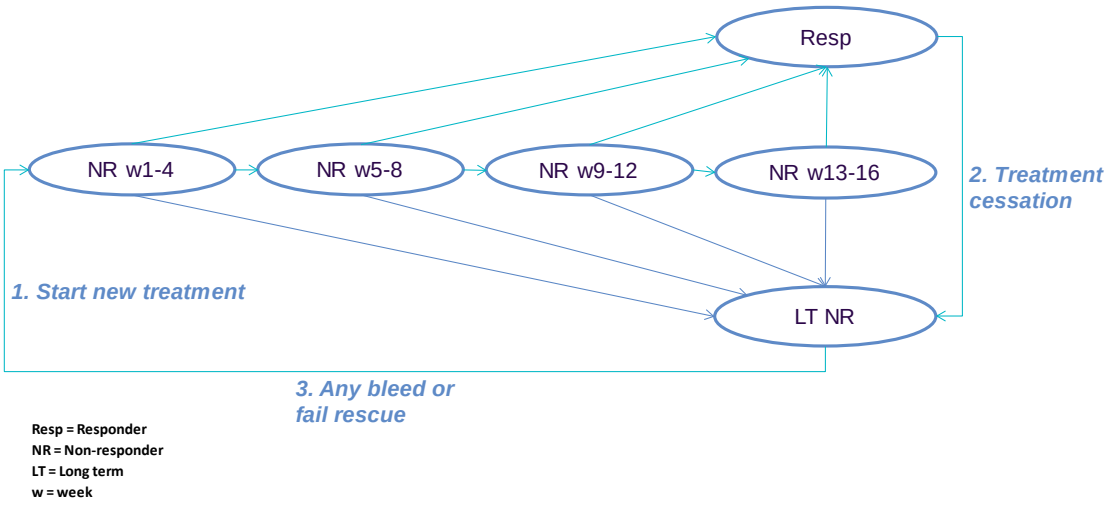
[11] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

The model simulates patients in six health states per treatment:

- Four tunnel states are used to model time to response. Within these tunnel states patients are assumed to be non-responders (platelets<50x10^9/L)
- Patients enter a long term responder state (platelets≥50x10^9/L) from the tunnel states if they respond; and
- A long term-non-responder state if they do not respond or if they lose response from the long-term responder state

Patients can die from general causes or from ITP-related death in any health state. The risk of death is driven by the risk of an inpatient bleed (see section 6.3.1).

Figure B17: Model Structure



Cost-effectiveness results for a base case and an alternative evaluation are presented.

- Base case: The base case incorporates a set of assumptions deemed most relevant to the decision problem. Where appropriate the assumptions from appraisal TA221 were used to relate short term trial data to lifetime costs and outcomes. The final recommendation for romiplostim was based on the general acceptance of these assumptions.
- Alternative evaluation: In this evaluation, alternative data from the eltrombopag trial program were used to inform assumptions relating to lifetime costs and outcomes. The most up to date sources of clinical evidence were also incorporated from an updated systematic review.

A sensitivity analysis incorporating all available assumptions from TA221 is provided in section 6.6.2.

Sources for the key inputs in the base case and the alternative evaluation are provided in Table B62.

Table B62: Description of source of model input parameters and justification for base case

	Base case	Alternative evaluation (if different to base case)	Justification of base case
Patient demographics	RAISE		Patients in the RAISE trial are reflective of a severe refractory cITP population.
Treatment pathway	As per the treatment pathway assumed in TA221 but with TPO-RAs positioned after rituximab in the sequence.		There is no defined treatment pathway for cITP and clinical practice varies considerably. With the exception of the positioning of rituximab, the treatment sequence is consistent with current clinical guidelines. These guidelines (published after romiplostim guidance was issued) suggest that rituximab is likely to be used before TPO-RAs. The treatment sequence is varied in sensitivity analyses.
Probability of receiving the different treatments in the pathway	Taken fromTA221 (Amgen physician survey). [75]		This assumption is consistent with that in TA221.[75] Treatment guidelines published after the romiplostim appraisal suggest that treatment practice is unlikely to have changed (apart from the positioning of rituximab) since the Amgen physician survey was conducted. There is no defined treatment pathway and given the heterogeneity in patients and the way they are treated, it was considered that a new survey would not alleviate this uncertainty.
Response rates	**Eltrombopag**: RAISE (probability of achieving a platelet response: platelets $\geq 50 \times 10^9$/L<400 $\times 10^9$/L) **Romiplostim**: Assumed equal to eltrombopag **Non TPO-RAs**: TA221 (Amgen systematic review).[75]	**Non TPO-RAs:** Updated GSK systematic review.	There is no evidence of a significant difference in efficacy between the TPO-RAs. Point estimates from the indirect comparison are applied in a sensitivity analysis. Response rates for non TPO-RAs are consistent with TA221. [75]

Time to response	**Eltrombopag**: RAISE. **Romiplostim**: TA221 (Kuter 2008).[60] **Non TPO-RAs**: TA221 (Amgen SR).[75]	**Non TPO-RAs**: GSK updated SR / or International Consensus Report where data not available from SR.	Eltrombopag and romiplostim have different methods of administration and it was therefore considered appropriate to use the time to response from the respective pivotal trials to account for the different pharmacokinetic profiles. Time to response for non TPO-RAs are consistent with TA221. [75]
Time on treatment	**Eltrombopag:** analysis of RAISE/EXTEND data. **Romiplostim**: Assumed equal to eltrombopag. **Non TPO-RAs:**TA221 (Amgen SR). [75]	**Non TPO-RAs**: Updated SR.	Equivalent time on treatment of the TPO-RAs is assumed, consistent with the assumption of no difference in efficacy. Although a similar analysis was conducted by Amgen, full details of this were not available therefore it is not possible to compare them. For non TPO-RAs time on treatment is consistent with TA221
Probability of bleeding for platelet counts > and < 50 x10^9/L	TA221 (estimated from available distribution parameters). [75]	Analysis of RAISE/EXTEND data.	Consistent with the assessment of romiplostim in TA221. [75]
Type of bleed requiring hospitalisations	RAISE/EXTEND.		Not available from TA221. [75]
ITP-related mortality (modelled on bleed rates)	Danese 2009.[17]		This approach is consistent with the assumption in TA221 that excess mortality risk results from bleeding events requiring hospitalisation. Data for TA221 was taken from an earlier cut of the data published by Danese 2009,[17] however as results did not differ significantly the 2009 publication has been used in the base case.
Probability of receiving rescue at platelet counts > and < 50 x10^9/L	TA221. [75]	RAISE/EXTEND.	Consistent with TA221. [75]
Type of rescue	TA221. [75]	RAISE/EXTEND. Platelet transfusions also included as	The proportions of different rescue medications used are consistent with TA221[75]. This assumption is explored

		rescue.	in sensitivity analyses.
AE rates	TA221. [75]		Consistent with TA221[75]. Eltrombopag assumed to be equivalent to romiplostim.
Utilities	Szende 2010[135]; a high quality vignette study in UK participants.		The Szende data is derived from UK participants and has good coverage of the relevant health states for the model. Use of SF-6D (mapped from SF36) data from RAISE/EXTEND is explored through sensitivity analysis.
Utility decrement for AEs	TA221. [75]		Consistent with TA221. The decrements used in TA221[75] are considered reasonable assumptions given the paucity of data from the GSK systematic review.
Dosing	**Eltrombopag**:RAISE/EXTEND. **Romiplostim:** Kuter 2008[60] (plateau dose maintained) **Non TPO-RAs**:Provan 2010[7] or TA221. [75]		The dose of romiplostim has been shown to increase over time therefore it is assumed that the mean dose at the end of the Kuter 2008 trial is maintained. The impact of using the modelled dose from TA221[75] is explored in a sensitivity analysis. Doses for non TPO-RAs are from the international consensus guideline. If details were not available or were not clear in the guideline they were taken from TA221. [75]
Costs	BNF/ NHS Reference costs.		BNF 63 and NHS reference costs 2010/11.

6.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

The cost-effectiveness model will compare three treatment sequences:

- Eltrombopag → non TPO-RA pathway
- Romiplostim → non TPO-RA pathway
- Non TPO-RA pathway

The non TPO-RA pathway comprises a sequence of non-TPO-RAs: rituximab, azathioprine, mycophenolate mofetil, ciclosporin, dapsone, danazol, cyclophosphamide, vincristine and

vinblastine.

The base case treatment pathway is illustrated as Figure B18. The sequence reflects that used in the manufacturer submission for TA221, with the exception of rituximab being removed in the base case analysis (i.e. assumed to be offered prior to TPO-RAs). Little guidance is available regarding the preferred sequencing of treatments in second and subsequent treatment lines for cITP[7], see section 2.4. However, clinical opinion and local UK guidelines consistently suggest that rituximab is most likely to be used ahead of a TPO-RA. This evidence is summarised below in Table B63. The positioning of rituximab following a TPO-RA is explored in a sensitivity analysis.

Table B63: Local guidance regarding use of rituximab in cITP

Local body and date of guidance	Guidance
Bedfordshire and Luton Joint Prescribing Committee, Jan 2011[34]	Recommends treatment with rituximab, and includes within the policy drivers "Disinvestment in alternative treatments which are costly e.g. alpha interferon, alemtuzumab, mycophenolate, romiplostim and eltrombopag". This appears to imply use of rituximab ahead of these treatments.
St George's Healthcare NHS, March 2011[35]	• 2nd line treatments recommended: rituximab, mycophenolate mofetil, danazol, dapsone, vinca alkaloids, cyclosporine A • 3rd line treatment with splenectomy or romiplostim (in patients who are elderly or contraindicated to splenectomy) • Patients relapsed or refractory to splenectomy: romiplostim

Figure B18: Treatment pathway used in the base case (patients also receive rescue therapy as needed throughout the model)

immuno(therapy) = azathioprine/Mycophenolate mofetil/Ciclosporin; cytotoxics = Cyclophosphamide / Vinca alkaloids (vincristine and vinblastine)

Patients have a probability of receiving each treatment in the pathway. These probabilities are from TA221[75] and are derived from a physician survey conducted by the manufacturer (July 2008). This survey was considered appropriate for the present appraisal for the following reasons:

- Amgen's survey was large and is directly relevant to UK clinical practice; 169 UK haematologists were included.
- Treatment guidelines published after the date of Amgen's survey (International Consensus Report and updated ASH guidelines) confirm that there is no definitive treatment pathway for cITP. As the guidelines recommend a range of treatment options at different lines of therapy and not a specific treatment sequence, there is no reason to expect that practice will have changed considerably since the survey was conducted.
- The variability in approach to treating cITP is acknowledged in the literature and in clinical opinion (section 2). A new survey would not increase certainty given this variability.

As there is uncertainty regarding both the treatment sequence patients would receive in practice and the interpretation of the Amgen physician survey data, the following alternative treatment sequences are considered in sensitivity analyses:

- Inclusion of rituximab post-TPO-RAs in order to reflect the base case analysis in TA221.
- Positioning of TPO-RAs as the last non rescue treatment in the pathway, assuming all other active treatments have been exhausted. Feedback from clinicians suggests this may be where TPO-RAs are sometimes used in practice.

6.2.4 Please define what the health states in the model are meant to capture.

The responder and non responder health states in the model aim to capture differences between pathways examined for the following outcomes:

- Bleeding
- The need for rescue treatment
- Quality of life
- Mortality
- Costs

Within the health states patients can experience the following events:

- **Outpatient bleeds** can occur in any state, although the probability is higher in states with platelets $<50x10^9$/L. Patients experiencing an outpatient bleed incur a utility decrement and cost. Patients experiencing an outpatient bleed whilst in the long term non-responder state are assumed to start a new line of treatment. Further detail on outpatient bleeds can be found in section 6.3.1.
- **Inpatient bleeds** can occur in any state, although as above the probability is higher in states with platelets $<50x10^9$/L. Patients experiencing an inpatient bleed incur a utility decrement and cost specific to the type of bleed experienced (see section 6.3.1). Patients experiencing an inpatient bleed whilst in the long term non-responder state are assumed to start a new treatment. Additionally, patients experiencing an inpatient bleed also face a risk of ITP-related death.

- **Rescue events** can occur from any state, although probability is again higher in states with platelets <50x10^9/L. Patients face a possibility of receiving rescue therapy in order to elevate their platelets rapidly and this is associated with a cost. Patients may or may not respond to rescue therapy; those who do not respond are assumed to commence a new line of non rescue treatment. Patients receiving rescue when their platelets are <50x10$^{9/}$L may respond and achieve a platelet level of ≥50x10^9/L, patients who receive rescue therapy and respond are assumed to experience the same rates of outpatient and inpatient bleeds as those responding to non rescue treatments. The model does not assume that rescue is dependent on bleeding.

Once all treatment options along the pathway have been exhausted, patients are assumed to remain in the long-term non-responder state. The model structure is depicted in Figure B17.

6.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

As highlighted in Section 2.1 the main feature of chronic ITP is an increased risk of bleeding events, in turn associated with an increased risk of mortality and poor quality of life. The model captures the time spent with a platelet count ≥50x10^9 which is associated with a reduced risk of bleeding. The structure is consistent with the primary objective of treatment in cITP, namely to achieve a platelet count associated with adequate hemostasis, thereby reducing serious bleeds.

Patients entering the model are assumed to be refractory to first line treatment with steroids or IVIg. Model inputs taken from the literature and pivotal trials relate to this refractory patient group in whom the TPO-RAs are licensed. Patients are assumed to start a new active treatment if they bleed or if they don't respond to rescue treatment.

Transition between the responder and non responder states occurs as a result of the response rate and the time on treatment for each treatment in the sequence. In practice these are the only factors that would influence movement through the treatment sequence.

6.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table B64: Key features

Factor	Chosen values	Justification
Time horizon	A lifetime time horizon has been used in the model. This has been set to 690 four week cycles (~53 years) after which time the proportion of patients remaining alive is negligible.	Consistent with NICE reference case.
Cycle length	The model uses four week (28 day) cycles.	Cycle length is practical given the modelled time horizon but should also be short enough to capture change in states over time. Patients are generally followed up on a monthly basis.
Half-cycle correction	A half cycle correction has been applied.	Consistent with NICE reference case.
Were health effects measured in QALYs; if not, what was used?	QALYs.	Consistent with NICE reference case.
Discount of 3.5% for utilities and costs.	Costs and effects have been discounted at 3.5% per annum.	Consistent with NICE reference case.
Perspective (NHS/PSS).	NHS.	Consistent with NICE reference case. No personal and social services costs have been identified.

Technology

6.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Eltrombopag and romiplostim are incorporated into the model as per their marketing authorization and using doses consistent with the respective SmPCs.

The dose of eltrombopag in the model is based on data from the RAISE trial, split by splenectomy status. In order to reflect the titration of dosing according to platelet response, doses are estimated for four week periods up to 23 weeks, beyond which the dose is assumed stable (based on the average dose at 24 weeks). These estimates are presented in Table B65 where it can be seen that the eltrombopag dose stabilises within the first four weeks. The base case therefore assumes that the post-24 week dosing (estimated from EXTEND data) for eltrombopag is maintained after this time point.

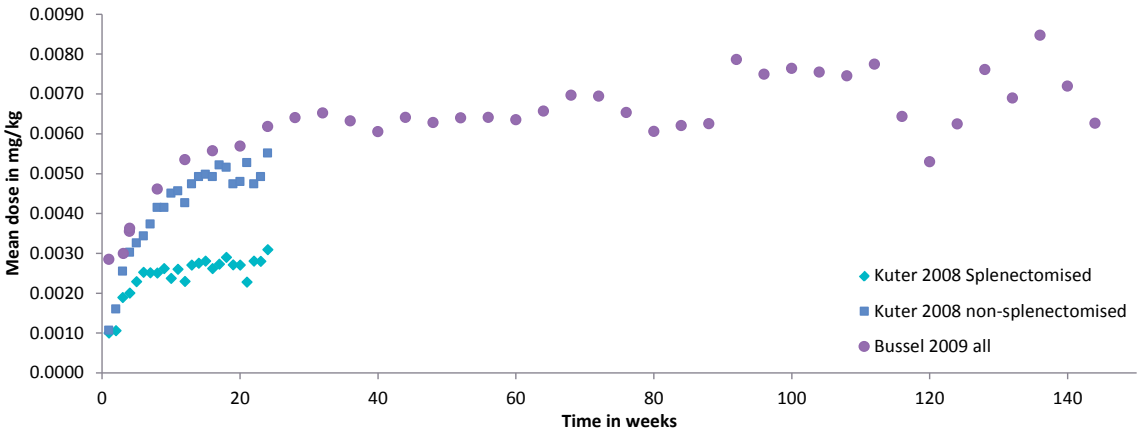
Table B65: Eltrombopag dosing used in model (mg)

Time period	Dose, splenectomised Mean (se)	Dose, non-splenectomised Mean (se)
Week 0-3	48.96 (1.244)	48.51 (0.873)
Week 4-7	56.81 (2.952)	54.62 (2.024)
Week 8-11	57.78 (3.114)	55.49 (2.195)
Week 12-15	56.871 (3.2)	55.12 (2.395)
Week 16-19	54.66 (3.38)	56.20 (2.210)
Week 20-23	57.35 (3.225)	57.13 (2.219)

Figure B19 shows the mean dose over time for Kuter 2008[60] and the extension study[61]. The dosing data for romiplostim was presented as graphs, so a graphical data extraction package was used to generate this figure (Techdig).

The same approach is taken to dosing of romiplostim in the model. The dose of romiplostim used in the base case of the model reflects the increase in the initial 24 weeks of use and is assumed to stabilise beyond 24 weeks at the last observed value. In the base case both the increase in dose and the stabalised adjusted doses from the Kuter 2008[60] trial will be used.

Figure B19: Mean dose over time for patients receiving romiplostim[60;61]



The dose from the romiplostim extension study is used in a sensitivity analysis. Data from the extension study was available only as a plot for all patients, so to model splenectomised and non-splenectomised patients separately, the ratio of dosing between these patients observed in Kuter 2008 is assumed to apply during the extension. The absolute dose for each group is derived using this information along with the proportion of splenectomised patients in the extension study (60%) as reflected in Table B66. In this analysis the dose beyond the 24 week period is estimated as the average from 24 weeks to the final follow-up.

Table B66: Romiplostim dosing used in model (mg)

	Kuter 2008[60]		Bussel 2009 extension+[61]	
Time period	Dose, splenectomised Mean*	Dose, non-splenectomised Mean	Dose, splenectomised Mean	Dose, non-splenectomised Mean
Week 0-3	0.00206	0.00149	0.00376	0.00220
Week 4-7	0.00365	0.00246	0.00435	0.00254
Week 8-11	0.00437	0.00247	0.00553	0.00323
Week 12-15	0.00489	0.00272	0.00642	0.00375
Week 16-19	0.00498	0.00276	0.00669	0.00390
Week 20-23	0.00511	0.00274	0.00682	0.00399
Post-week 24	0.00511	0.00274	0.00809	0.00472

* Note s.e.'s reported on weekly basis; + Using assumption that ratio of dosing between splenectomised and non-splenectomised patients is as per Kuter 2008[60]

In addition, as romiplostim is supplied as vials, and there are too few patients per centre to anticipate any vial sharing, drug wastage needs to be modelled. This is captured in the analysis by calculating the number of vials each patient in RAISE would require (based on each individuals baseline weight) in order to deliver the target dose.

Non-TPO drug dosing

The modelled doses and the length of time that patients receive non TPO-RAs are derived either from Provan 2010,[7] the International Consensus Report that provides consensus based recommendations relating to treatment of ITP in adults or from the manufacturer submission for TA221[75] if insufficient information was provided in the guideline (Table B67).

Table B67: Regimens and treatment durations for non-TPO treatments (BNF 63[136])

Drug	kg or m^2	Treatment regimen:Dose/kg or m^2/mg	Frequency per 4 week cycle	Route	Duration days	Source
Rituximab	m^2	375	4	Infusion	28	Provan 2010
Azathioprine	Kg	1.5	28	Tablet	28	TA221
Mycophenolate mofetil	Na	1000	56	Tablet	24.5	Provan 2010
Ciclosporin	Kg	5	28	Tablet	28	TA221
Dapsone	Na	87.5	28	Tablet	28	
Danazol	Na	200	84	Tablet	28	
Cyclophosphamide	Kg	1.5	28	Tablet	112	Provan 2010
Vincristine	Na	1.5	4	Injection	28	
Vinblastine	Na	10	4	Injection	21	
Rescue – IVIg	Kg	1000	28	Infusion	1.5	
Rescue – Anti-D	Kg	0.0625	28	Infusion	2	
Rescue – IV steroid	Kg	1.25	28	Injection	3	TA221

6.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

No continuation or stopping rules are assumed in the economic model. Please refer to 6.3.1 for details regarding the time spent on treatment for each therapy.

6.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

6.3.1 Please demonstrate how the clinical data were implemented into the model.

The following sections outline how the clinical data have been incorporated into the model in the base case and in the alternative evaluation (where this differs from the base case). The parameters used in the base case are summarised in Table B68. Parameters for the alternative evaluation can be found in Appendix 14.

Response rates – base case

TPO-RAs

The response rate for eltrombopag has been taken directly from the RAISE study. The primary outcome in RAISE was the odds of achieving a platelet count ≥50 x 10^9 and ≤400 x 10^9/L during the six-month treatment period, for subjects receiving eltrombopag relative to placebo (section 5.5.3). The response rate was obtained from this data by assigning a response status to patients who met this crierion at least once during the relevant period.

The base case assumes that there is no difference in efficacy between the TPO-RAs and hence the same rate of response has been applied to romiplostim. This assumption is considered appropriate given the uncertainty associated with the results of an indirect comparison of eltrombopag versus romiplostim and the fact that the TPO-RAs are considered interchangeable in clinical practice.[7] The indirect treatment comparison, including the rationale and interpretation, is discussed in detail in section 5.7. In summary, a post hoc analysis of RAISE data derived response (sustained/durable and overall response at six months) and bleeding data for eltrombopag that showed no significant differences to romiplostim. However, the design of the clinical trials was not identical and any comparisons that were made will be associated with uncertainty. This is compounded in this orphan disease area by the small size of the trials and the low event rates for some outcomes, in some arms. A supplementary analysis summarised below illustrates how sensitive the results of the indirect treatment comparison are to the placebo rates in Kuter 2008[60]:

- For durable response, the indirect comparison point estimates favour eltrombopag when the number of events in the placebo arm of Kuter 2008[60] is increased by ≥1 (splenectomised group) and ≥2 (non-splenectomised or pooled groups).
- For overall response the point estimate of the odds ratio approaches 1.0 as the number of events in the placebo arm increases in both subgroups.
- For both durable and overall response in all groups the confidence intervals become very wide as the number of placebo responses increases.

Two sensitivity analyses are included to explore the impact of varying the assumptions of efficacy:

- Using the post-hoc definition of overall response for eltrombopag (see section 5.5.3), but retaining the assumption of equivalent efficacy of the TPO-RAs and;
- Using the point estimates derived from the indirect comparison to inform relative efficacy with respect to overall response.

Non TPO-RAs: The base case analysis takes response rates for non TPO-RA comparators from TA221. These were derived from a systematic review conducted by Amgen.

Response rates – alternative evaluation

TPO-RAs: As per base case.

Non TPO-RAs: Response rates for non TPO-RA comparators in the alternative evaluation are the weighted average response rates for each treatment as determined in the GSK systematic review and quantitative analysis for each comparator (see section 5.8.12). There is insufficient data available in the literature to estimate response rates specific to splenectomised and non-splenectomised patients. In order to reflect the differential prognosis of these patients it was therefore assumed that in the non TPO-RA studies the relative risk for response in splenectomised compared to non-splenectomised patients was as estimated for the primary end point of RAISE. A treatment-specific probability of response by splenectomy status could then be estimated using this relative risk and assuming a similar proportion of patients were splenectomised in the non TPO-RA studies as in RAISE (37%).

Time to response – base case

TPO-RAs*:* The modelled time to response for eltrombopag is derived from RAISE data and reflects the time at which the proportion responding to eltrombopag stabilises, at 15 days.[39] For romiplostim the maximum time from treatment initiation to initial response is assumed to be 4 weeks, reflecting that seen in the Kuter trials.[60]

Non-TPO-RAs: Time to response for the non-TPO treatments are taken from TA221.

Time to response – alternative evaluation

TPO-RAs: As per base case.

Non TPO-RAs: Time to response is derived from the GSK systematic review and quantitative analysis (see section 5.8.12).

Data on time to response do not differentiate between splenectomised and non-splenectomised patients as insufficient data was available to permit this. The model assumes that the time to response is the same in these two patient groups.

Time on treatment – base case

TPO-RAs: Time on treatment for eltrombopag is based on actual treatment cessation data from RAISE and EXTEND, where time on treatment is modelled as a survival variable. The methods used to estimate time on treatment from patient level data are detailed in appendix 15.

This analysis has only been run for and applied to patients achieving a response. Non-responders are assumed to experience the cost of TPO-RAs for one cycle only, by which point it is expected that response will be assessable and patients not achieving response will be taken off treatment.

A sensitivity analysis which includes all patients (rather than just those who achieve a response) who remain on treatment is also provided. This may be more applicable to clinical practice where a wider set of considerations are likely to be employed to determine treatment continuation (e.g. absence of bleeding symptoms).

In the base case the time on treatment for romiplostim is assumed to be equal to that for eltrombopag. Although it is possible to derive mean time on treatment from the TA221 documents,[75] the methods used to derive this estimate are marked as commercial in confidence in the manufacturer submission, and the distributional form and parameters of the survival curve used are not reported. These data cannot therefore be robustly compared with the eltrombopag data. Additionally, the analysis conducted for TA221 was not split by splenectomy status. The eltrombopag data suggests that splenectomy status is be a determinant of time on treatment.

Non TPO-RAs: Time on treatment is taken from TA221.

Time on treatment – alternative evaluation

TPO-RAs*:* As per base case.

Non TPO-RAs*:* Time on treatment is taken from the systematic review and quantitative analysis conducted by GSK (Section 5.8). In the absence of robust data and in order to avoid increasing the model complexity, time on treatment is assumed to follow an exponential distribution for all non TPO-RA comparators.

Risk of bleed

The risk of bleeding in the model is based on platelet level and as such is independent of treatment. Patients in responder states face a risk of outpatient bleeds, whilst patients in non-responder states face the risk of both outpatient bleeds and bleeds requiring hospitalisation. The types and proportions of hospitalised and outpatient bleeds were estimated from RAISE/EXTEND (see appendix 15 for more information).

In line with TA221 in the base case it is assumed that once patients enter the final non-responder state (i.e. are refractory to all prior therapies) their rate of inpatient bleeds doubles. This assumption is explored through sensitivity analysis.

Base case: Bleed rates conditional upon platelet count from TA221 were used. These were derived from the probabilistic parameters reported in TA221.

Alternative evaluation: Bleeding rates conditional upon platelet count were derived from RAISE/EXTEND data. The number of events experienced per unit time conditional on platelet count was estimated as the number of events divided by the total time with the required platelet level ($\geq 50 \times 10^9$ and $< 50 \times 10^9$/L) from RAISE and EXTEND (placebo and eltrombopag arms pooled). This was estimated for splenectomised, non-splenectomised, and for all patients. The methods used to estimate bleed rates are documented in Appendix 15.

Mortality – base case and alternative evaluation

All cause mortality is modelled using interim life tables (2007-2009) from the Office for National Statistics and depends upon the patient's gender and current age in the model as derived from mean age and gender split in the RAISE trial.

ITP-related mortality is modelled based on bleed rates. Treatment therefore impacts mortality by affecting the amount of time spent in the non-responder states and thus bleed rates. A mortality rate is applied to each bleed requiring hospitalisation, with mortality specific to the type of bleed. These rates are from Danese et al 2009.[17] Three bleed categories are considered representative of the types of bleed requiring hospitalisation in RAISE and EXTEND: gastrointestinal bleeds, intracranial haemorrhage and coagulation disorder (other). The mortality rates associated with these bleed types are applied to patients experiencing a bleed related hospitalisation in the model, in proportion to the number of patients experiencing each bleed type in RAISE and EXTEND (see appendix 15).

In a sensitivity analysis mortality has been modelled conditional upon patient platelet level.

Risk of rescue

Base case: Assumptions about the rate and type of rescue given to patients with platelet levels below 50 x 10^9/L have been taken from TA221. In the base case, rescue was considered to be IVIg, anti-D or IV corticosteroids. The type of rescue medication and the proportions in which they would be used were derived from a survey of physicians undertaken by Amgen for TA221.

Alternative evaluation*:* The number of rescue events per unit time was estimated for patients with platelet levels above and below 50x10^9/L in RAISE/EXTEND. In addition to IVIg, anti-D and IV corticosteroids, platelet transfusions were also considered to be a rescue treatment. The estimation of rates of rescue from EXTEND and RAISE are described fully in Appendix 15. In order to reflect the likely rescue strategies in the UK all analyses of rescue data from RAISE/EXTEND were limited to countries with a per capita health care expenditure of >$2,000 per year. As reflected by analyses of individual patient data in appendix **Error! Reference source not found.**, a clear distinction in the use of rescue therapy was seen in these countries. The proportion in which the different rescue medications were used was also derived from RAISE/EXTEND (Appendix 15).

Adverse events – base case and alternative evaluation

In the model adverse events were grouped as either severe adverse events or other adverse events.

TPO-RAs: The adverse event rates for the two TPO-RAs were assumed to be equivalent and were taken from TA221.

Non TPO-RAs: Adverse event rates were taken from TA221 as the systematic review conducted by GSK identified minimal data regarding toxicity.

6.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Transition between the responder and non-responder health states in the model is dependent on treatment response rates, time to treatment response and duration of response. For all treatments in the modelled sequences, these parameters are derived from the clinical data and literature as discussed in section 6.3.1 above.

6.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

The model assumes transition probabilities do not vary over time. This is an considered an appropriate assumption given that there is currently no robust evidence to suggest that ITP is a progressive disease.

6.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Bleeding events and the use of rescue treatments are dependent on whether a patient is in a responder or non responder health state (i.e. has platelets ≥50 $x10^9$/L or <50 $x10^9$/L). Gernsheimer et al (2010)[18] report a strong association between platelet count and bleeding events where bleeding events were found to be most highly concentrated at platelet levels <20 $x10^{9/}$/L. This is further supported by analysis of the RAISE/EXTEND data which suggests a similar relationship between platelet level and bleeding (see Appendix 15).

The analysis assumes that ITP related mortality is associated with serious bleeding events that require hospitalisation. This is described in further detail in section 6.3.1 above and in section **2**. A sensitivity analysis is included that explores modelling mortality conditional on platelet count. This approach was not used in the base case as a result of the very low event rates in the clinical trials.

6.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[12]:

Informal clinical opinion was sought to inform the clinical appropriateness of the modelling approach. Input parameters are derived from trial data, published literature or from NICE appraisal documentation.

Summary of selected values

6.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Variables included in the cost-effectiveness analysis are provided in Table B68. Variables used for the alternative evaluation can be found in Appendix 15.

[12] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table B68: Base case model inputs

Variable	Value Splenectomised	Distribution	Alpha	Beta	Value non-splenectomised (if different)	Distribution	Alpha	Beta	Reference
Patient demographics									
Age	47.91								RAISE[39] see section 5.5.3
Male:female ratio	69% female								
Average weight	74.22Kg								
Average body surface area	1.82m^2								
Treatment Pathway (probability of receiving each treatment)									
Rituximab (excluded from base case)	100%	Beta							TA221[75]
Aziothiaprine	59%	Beta	16.97	11.87					
Mycophenolate mofetil	37%	Beta	26.64	45.92					
Ciclosporin	4%	Beta	21.80	526.47					
Danazol	7%	Beta	21.76	23.67					
Dapsone	48%	Beta	65.96	880.16					
Cyclophosphamide	2%	Beta	41.91	2318.96					
Vinca alkaloids	5%	Beta	40.36	717.48					

Variable	Value Splenectomised	Distribution	Alpha	Beta	Value non-splenectomised (if different)	Distribution	Alpha	Beta	Reference
Response rates									
Eltrombopag	76%	Beta	0.68	0.17	80%	Beta	0.38	12	RAISE
Romiplostim	76%	Beta	0.68	0.17	80%	Beta	0.38	12	Assumption
Rituximab (excluded from base case)	58%	Beta	17.48	12.81	58%	Beta	17.48	12.81	TA221[75]
Azathioprine	63%	Beta	26.18	15.50	50%	Beta	20.84	20.84	
Mycophenolate mofetil	44%	Beta	7.35	9.35	57%	Beta	9.44	7.26	
Ciclosporin	63%	Beta	26.34	15.34	50%	Beta	20.84	20.84	
Dapsone	47%	Beta	9.27	10.57	50%	Beta	10.65	9.19	
Dapsone	60%	Beta	30.34	20.22	45%	Beta	22.9	27.66	
Cyclophosphamide	61%	Beta	10.62	6.68	70%	Beta	12.11	5.19	
Vinca alkaloids	53%	Beta	10.70	9.33	67%	Beta	13.42	6.61	
Rescue – IVIg	79%	Beta	6.49	1.77	81%	Beta	6.54	1.72	
Rescue - Anti-D	0%	Beta	NA	NA	46%	Beta	22.61	26.59	
Rescue - IV steroid	46%	Beta	22.63	26.57	46%	Beta	22.632	26.57	
Rescue - platelet transfusion	N/A								

Variable	Value Splenectomised	Distribution	Alpha	Beta	Value non-splenectomised (if different)	Distribution	Alpha	Beta	Reference
Time to response (days)									
Eltrombopag	15.0	Gamma	16.000	0.938					RAISE CSR[39] p64, % responders to eltrombopag stabilizes after 15 days
Romiplostim	28.0	Gamma	16.000	1.750					Kuter 2008,[60] median platelet counts over time suggest that response stabilizes after 4 weeks
Rituximab (excluded from base case)	56.0	Gamma	16.000	3.500					TA221[75]
Azathioprine	112.0	Gamma	16.000	7.000					
Mycophenolate mofetil	112.0	Gamma	16.000	7.000					
Ciclosporin	56.0	Gamma	16.000	3.500					
Dapsone	28.0	Gamma	16.000	1.750					
Dapsone	112.0	Gamma	16.000	7.000					
Cyclophosphamide	56.0	Gamma	16.000	3.500					
Vinca alkaloids	28.0	Gamma	16.000	1.750					
Rescue – IVIg	Instantaneous								
Rescue - Anti-D	Instantaneous								
Rescue - IV steroid	Instantaneous								
Rescue - platelet transfusion	Instantaneous								

Variable	Value Splenectomised	Distribution	Alpha	Beta	Value non-splenectomised (if different)	Distribution	Alpha	Beta	Reference
Time on treatment (days)									
Eltrombopag	See appendix 15								RAISE/EXTEND
Romiplostim	Assumed equal to eltrombopag								Assumption
Rituximab (excluded from base case)	575.27	Gamma	16.00	35.95					TA221[75]
Azathioprine	617.88	Gamma	16.00	38.62					
Mycophenolate mofetil	173.49	Gamma	16.00	10.84					
Ciclosporin	493.09	Gamma	16.00	30.82					
Dapsone	617.88	Gamma	16.00	38.62					
Danazol	4484.97	Gamma	16.00	280.31					
Cyclophosphamide	821.81	Gamma	16.00	51.36					
Vinca alkaloids	42.61	Gamma	16.00	2.66					
Rescue – IVIg	28.00								
Rescue - Anti-D	28.00								
Rescue - IV steroid	28.00								
Probability of bleed (per 4 week cycle)									
Platelets >50,000 - Inpatient bleed	Assumed zero								TA221[75] (estimated from probabilistic parameters of beta distribution)
Platelets > 50,000 - outpatient bleed	0.071	Beta	39.6	517.8					
Platelets <50,000 - Inpatient bleed	0.043	Beta	40.8	919.8					
Platelets <50,000 - outpatient bleed	0.455	Beta	22.8	27.3					

Variable	Value Splenectomised	Distribution	Alpha	Beta	Value non-splenectomised (if different)	Distribution	Alpha	Beta	Reference
Mortality rates									
Other bleed	1.7%	Beta	551	31888					Danese 2009[17]
GI haemorrhage	4.6%	Beta	109	2257					
Intracranial haemorrhage	13.2%	Beta	260	1706					
Frequency of bleeds requiring hospitalisation									
Platelets <50,000 % bleeds requiring hospitalisation									
Other bleed	63%								RAISE/EXTEND
GI haemorrhage	19%								
Intracranial haemorrhage	19%								
Platelets >50,000 % bleeds requiring hospitalisation									
Other bleed	71%								RAISE/EXTEND
GI haemorrhage	29%								
Intracranial haemorrhage	0%								
Rate of rescue (per 4 week cycle)									
Platelets >50 x 10^9	0%				0				TA221[75]
Platelets<50 x10^9	68%	Beta	14.28	6.72	33%	Beta	6.93	14.07	
Distribution of rescue type									
Platelets <50,000									
IVIg	0.64	Dirichlet			0.59	Dirichlet			TA221[75]
Anti-D	0.00	Dirichlet			0.25	Dirichlet			
IV Steroid	0.36	Dirichlet			0.16	Dirichlet			
Platelet transfusion	0.00	Dirichlet			0.00	Dirichlet			

Variable	Value Splenectomised	Distribution	Alpha	Beta	Value non-splenectomised (if different)	Distribution	Alpha	Beta	Reference
Serious adverse event rates									
Eltrombopag	0.03	Gamma	41.37	1337.76					TA221[75]
Romiplostim	0.03	Gamma	41.37	1337.76					
Rituximab (excluded from base case)	0.03	Gamma	41.37	1337.76					
Azathioprine	0.15	Gamma	36.13	204.75					
Mycophenolate mofetil	0.15	Gamma	36.13	204.75					
Ciclosporin	0.15	Gamma	35.69	187.4					
Dapsone	0.11	Gamma	37.88	306.48					
Dapsone	0.16	Gamma	36.13	204.75					
Cyclophosphamide	0.21	Gamma	33.51	126.06					
Vinca alkaloids	0.21	Gamma	33.51	126.06					
Rescue – IVIg	0.02	Gamma	2.10	97.90					
Rescue - Anti-D	0.03	Gamma	2.80	97.20					
Rescue - IV steroid	0.03	Gamma	3.00	97.00					
Rescue - platelet transfusion	0.03	Gamma	3.00	97.00					Assumption

Variable	Value Splenectomised	Distribution	Alpha	Beta	Value non-splenectomised (if different)	Distribution	Alpha	Beta	Reference
Other adverse event rates									
Eltrombopag	0.31	Gamma	29.14	64.87					TA221[75]
Romiplostim	0.31	Gamma	29.14	64.87					
Rituximab (excluded from base case)	0.00	Gamma	0.00	0.00					
Azathioprine	0.24	Gamma	32.20	101.97					
Mycophenolate mofetil	0.24	Gamma	32.20	101.97					
Ciclosporin	0.24	Gamma	27.39	50.88					
Dapsone	0.24	Gamma	32.20	101.97					
Dapsone	0.35	Gamma	32.20	101.97					
Cyclophosphamide	0.30	Gamma	29.58	69.02					
Vinca alkaloids	0.30	Gamma	29.58	69.02					
Rescue – IVIg	0.00	Gamma	NA	NA					
Rescue - Anti-D	0.00	Gamma	NA	NA					
Rescue - IV steroid	0.70	Gamma	70.00	30.00					
Rescue - platelet transfusion	0.00	Gamma	NA	NA					
Utilities									
No bleed, sufficient platelets	0.86	1-gamma							Szende 2010
Bleed, sufficient platelets	0.73	1-gamma							
No bleed, low platelets	0.84	1-gamma							
Bleed, low platelets	0.73	1-gamma							
Intracranial hemorrhage (2-6 months)	0.04	1-gamma							
Steroid treatment adverse events	0.76	1-gamma							
Gastrointestinal bleed	0.45	1-gamma							
Other bleed requiring inpatient	0.45	1-gamma							

Variable	Value Splenectomised	Distribution	Alpha	Beta	Value non-splenectomised (if different)	Distribution	Alpha	Beta	Reference
Utility decrements with Serious AEs									
Eltrombopag	0.10	1-gamma	1296.00	0.001					TA221[75]
Romiplostim	0.10	1-gamma	1296.00	0.001					
Rituximab	0.10	1-gamma	1296.00	0.001					
Azathioprine	0.40	1-gamma	36.00	0.017					
Mycophenolate mofetil	0.40	1-gamma	36.00	0.017					
Ciclosporin	0.40	1-gamma	36.00	0.017					
Dapsone	0.40	1-gamma	36.00	0.017					
Danazol	0.40	1-gamma	36.00	0.017					
Cyclophosphamide	0.40	1-gamma	36.00	0.017					
Vinca alkaloids	0.40	1-gamma	36.00	0.017					
Rescue – IVIg	0.10	1-gamma	1296.00	0.001					
Rescue – Anti-D	0.10	1-gamma	1296.00	0.001					
Rescue – IV steroid	0.10	1-gamma	1296.00	0.001					
Rescue - platelet transfusion	0.10	1-gamma	1296.00	0.001					
Utility decrement for other AEs	0.1								

6.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.

Eltrombopag

Assumptions have been made in order to extrapolate the costs and outcomes of treatment over the lifetime horizon. Time on treatment for eltrombopag is based on actual treatment cessation data from RAISE/EXTEND where time on treatment is modelled as a survival variable (see Appendix 15). The Kaplan-Meier plot in Figure B20 provides a graphical representation of the risk of coming off treatment at any given time point, derived using the total time on treatment of all patients across the RAISE and EXTEND trials. The median observed time on treatment for all patients was [redacted]

[redacted]

An adjusted parametric analysis was conducted to analyse the effect of splenectomy on time-on-treatment, and to enable estimation of time-on-treatment beyond the combined duration of the RAISE and EXTEND trials. Further details of these analyses and the goodness of fit of six parametric curves to the empirical data are provided in Appendix 15. The lognormal distribution was considered to provide the superior fit to the empirical data and was chosen for modelling time on treatment of all patients when adjusting for splenectomy (see Figure B21).

[redacted]

Romiplostim

The base case assumes that the time on treatment for romiplostim is equal to that for eltrombopag. This is consistent with the assumption of equivalent efficacy of the TPOs.

The distributional form and parameters of the survival curve used to estimate time on treatment for romiplostim in TA221 were not available so it is not possible to robustly compare to the eltrombopag data or use this data in the base case. Furthermore the analysis for TA221 was not split by splenectomy status which, as shown by the eltrombopag data presented above, is a key determinant of time spent on treatment.

Non-TPOs

For non-TPOs, time on treatment is taken from the literature. In the base case, the results from Amgen's systematic review are used and are assumed to follow a gamma distribution.

6.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Assumption	Justification
The most appropriate treatment sequence is assumed to be: (TPO-RA)>immunotherapy > danazol > dapsone > cytotoxics > rescue as required	The lack of evidence based treatments for ITP and of recommendations for a definitive treatment sequence has been highlighted previously. The base case treatment sequence is consistent with the approach taken by the manufacturer in TA221 but incorporates more recent evidence concerning the use of rituximab, positioning it before treatment with TPOs.
TPO-RAs are the treatment of choice following an inadequate response to corticosteroids or IVIg.	TPO-RAs are one of several 2nd line treatment options recommended by international guidelines. There is no defined treatment pathway for ITP and practice in the UK varies widely. The positioning of TPO-RAs along the pathway is explored through sensitivity analysis.
Platelet level is a reasonable surrogate for requiring rescue therapy, and experiencing moderate and major bleeding events.	Analysis of the RAISE and EXTEND data suggest a strong relationship between platelet level and bleeding and between platelet level and the need for rescue therapy .
Major bleeding events are a reasonable surrogate for mortality.	Patients with cITP can experience serious bleeds. A large US study [17] demonstrates the association between severe bleeds and mortality. A sensitivity analysis exploring the impact of modeling mortality conditional on platelet level is provided.
Patients with severe and highly refractory cITP will eventually run out of treatment options to maintain their platelet levels. After this they will be monitored and if necessary given rescue treatment.	This is consistent with clinical feedback and is also consistent with the approach accepted in TA221.
Response to therapy is assumed to be equivalent to achieving a platelet count greater than $50x10^9$/L which is assumed to be maintained throughout treatment.	This threshold is the most commonly reported within the literature. A lower threshold may be more relevant to clinical practice but there is a lack of data on the proportion of patients reaching lower thresholds for comparator treatments.
When moving to a new active treatment, only a proportion of patients will receive each treatment in the pathway. Patients will not receive every available therapy.	This is consistent with the survey conducted for TA221. Although there is no defined treatment pathway for ITP and practice varies widely in the UK this is thought to reflect clinical practice as closely as possible.
Patients are at risk of requiring/receiving rescue medication depending on a platelet threshold.	This assumption is consistent with the management of patients experiencing a bleed or at high risk of bleeding. A high use of rescue medications was reported in both TPO-RA trials. Use of rescue medications such as IVIg have been found to be a major contributor to the total costs of managing chronic ITP patients. Case studies from 5 chronic ITP patients collated from UK haematologists for this submission also highlight the frequent use of rescue

Assumption	Justification
	medications.
Romiplostim is assumed to have equivalent safety and efficacy to that of eltrombopag.	No head to head evidence of romiplostim and eltrombopag is available. Indirect evidence is uncertain but suggests no significant differences between the two. The two products have identical licences and are treated as interchangeable by clinicians and in guidelines.
Several assumptions from TA221 have been used in the base case.	This enables eltrombopag to be assessed using similar assumptions to those underlying the assessment recommendation of romiplostim in TA221. An alternative evaluation in which data from a systematic review and analyses of the RAISE/EXTEND trial data is incorporated into the model is also presented.

6.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

6.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Patients with ITP are at increased risk of bleeding when they have low platelet levels; serious bleeding can significantly impact on a patient's quality of life as a result of hospitalizations. Further to this, ITP-related fatigue and the anxiety associated with the risk of bleeding have been shown to have a detrimental impact on quality of life[24;26;27]. Additionally, some patients express concern at increased susceptibility to infection as a result of some treatments (splenectomy, coriticosteroids).[24] Side-effects associated with ITP treatments may also impact on patients' quality of life. Of particular note are those associated with long term corticosteroid use; weight gain/increased appetite, changes in personality/mood/emotions, sleep problems, and moon face/puffy cheeks.[29]

A negative impact on reproductive health in women with ITP has also been reported, such as loss of libido due to symptoms of ITP and side effects of treatment, and concerns regarding exacerbation of menstrual bleeding, leading to seriously diminished QoL.[27;137]

GSK approached several ITP specialists with a request to collect descriptive patient case studies for the purpose of inclusion within this NICE submission. Five case studies of patients with cITP were received which demonstrate the impact of the disease on their mental and physical health (Appendix 13). The side effects as a result of receiving ITP treatments as well as the impact on the quality of life are also described. The impact on the ability to play sport or plan holidays due to uncontrolled symptoms is also described, as well as the anxiety associated with the uncertainty of fluctuating platelet levels. These case studies also demonstrate that patients with ITP respond to a treatment for a period of time, before relapsing and then are considered for other treatment options (consistent with the approach to treatment described in international treatment guidelines). For patients who are uncontrolled on treatment, rescue therapy, including IVIg, is often prescribed, and the case studies demonstrate that at least for some patients, IVIg is prescribed repeatedly over the course of a year.

6.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

The clinical manifestation of ITP is highly variable.[7] The disease is not progressive so HRQL is governed by response to treatment.[24-26] Patients who respond to therapy may experience side effects associated with their therapy at the same time as their bleeding is controlled while bleeding will affect patients who do not respond to treatment. Patients with chronic ITP may suffer adverse events associated with prolonged corticosteroid treatment, and with time the detrimental effects of corticosteroids may be difficult to endure. HRQL improves in these patients following withdrawal from corticosteroid treatment.[29]

HRQL data derived from clinical trials

6.4.3 If HRQL data were collected in the clinical trials identified in section 5 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

Quality of life data from the pivotal trials for eltrombopag and romiplostim are reported in the literature.[38;138]

In the RAISE study [38], quality of life was assessed using the SF-36 questionnaire. Disease specific QoL symptoms were also measured: fatigue was measured with the fatigue subscale of the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue questionnaire, the effect of bleeding on QoL was assessed with a 6-item subset from the THrombocytopenia Functional Assessment of Cancer Therapy- (FACT-TH6) questionnaire and changes to physical and mental energy were measured on the Motivation and Energy Inventory Short Form (MEI-SF) questionnaire.

Statistically significant improvements from baseline were shown for patients receiving eltrombopag compared with placebo for the physical role, vitality, emotional role, and the mental component summary scores of the SF-36 and the FACT-Th6 score. No significant changes were reported for any other QoL measures. Results of SF-36 from RAISE and EXTEND were mapped to SF-6D for use in modeling. The methods and results of the mapping are discussed in section 6.4.4 below.

George et al. (2009)[138] reported the QoL data assessed in the two romiplostim trials. QoL was recorded on the disease specific ITP-patient assessment questionnaire (PAQ) instrument. Data pooled from the two trials, adjusted for splenectomy status, showed statistically significant improvement for romiplostim-treated patients in six of the ten ITP-PAQ scales; symptoms, bother, activity, fear, social activity and women's reproductive health. The Kuter trial also collected EQ-5D data and this is reported by Sanz, 2011.[139] Sanz is discussed further in Section 6.4.6.

Only the SF-36 data collected in RAISE (and the extension study – EXTEND) and the EQ-5D data collected in Kuter 2008[60] can be converted to utilities that are compatible with the NICE reference case (derived from patients, and valued using a sample of the general population and a choice-based method).The mapping exercise and the publication of EQ-5D data from the romiplostim studies (Sanz, 2011)[139] are described in detail below.

Mapping

6.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

A mixed model was used to predict utility for patients with a given set of characteristics specified in the health states in the model using SF-36 data from RAISE/EXTEND that had been mapped to SF-6D scores and corresponding utility data (using the most recent Brazier algorithm [140]). Utility was related to the following predictors in this analysis: baseline utility, splenectomy status, platelet level and proximity to an outpatient bleed in a repeated measures model. Analyses were limited to observations that had non-missing data for the SF-36 assessments and for the potential predictor variables of interest. The final analytic dataset consisted of 1809 observations from 187 patients. As these analyses were not available in time to incorporate into the alternative evaluation the resulting utility scores were utilized in a sensitivity analysis. The results of the base case analysis do not change substantively following inclusion of these utility data.

HRQL studies

6.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 9.12, appendix 12.

The systematic review of HRQL data was incorporated into the systematic searches conducted to identify relevant clinical information. Search terms included general descriptors including *quality of life*, *quality of wellbeing* and *HRQL*, alongside terms to identify HRQL measurement (SF-36). Further details of the search strategy are provided in Appendix 2. The quality of life data reported in the pivotal trials for the TPO-RAs is discussed in section 6.4.3.

A separate systematic search of the literature was carried out to identify utility values for ITP health states to inform the modelling. The following databases were searched on the 16th March 2012: Embase, Medline and Medline-in-process, Econlit and NHS EED. Full details of the utility search strategies are included in Appendix 17.

Where appropriate search strategies included controlled vocabulary terms applicable to the particular database. Free-text terms were used in all searches. The controlled vocabulary used was MeSH terms in Medline, Medline in process, and NHS EED; Emtree terms in Embase. The search in Econlit comprised free-text terms for ITP only as subject headings used in this database are not relevant to this search for HRQL data and this database contain references to economic literature only. The search strategies in Medline, Medline in process, Embase, and NHS EED included terms for ITP and a filter to identify HRQL studies. All searches were limited to 2009 and onwards.

The previous NICE submission for eltrombopag and the submission for romiplostim were searched for pre-2009 data as it was anticipated that all relevant utility scores would have been identified by these submissions.

The inclusion criteria were as follows:

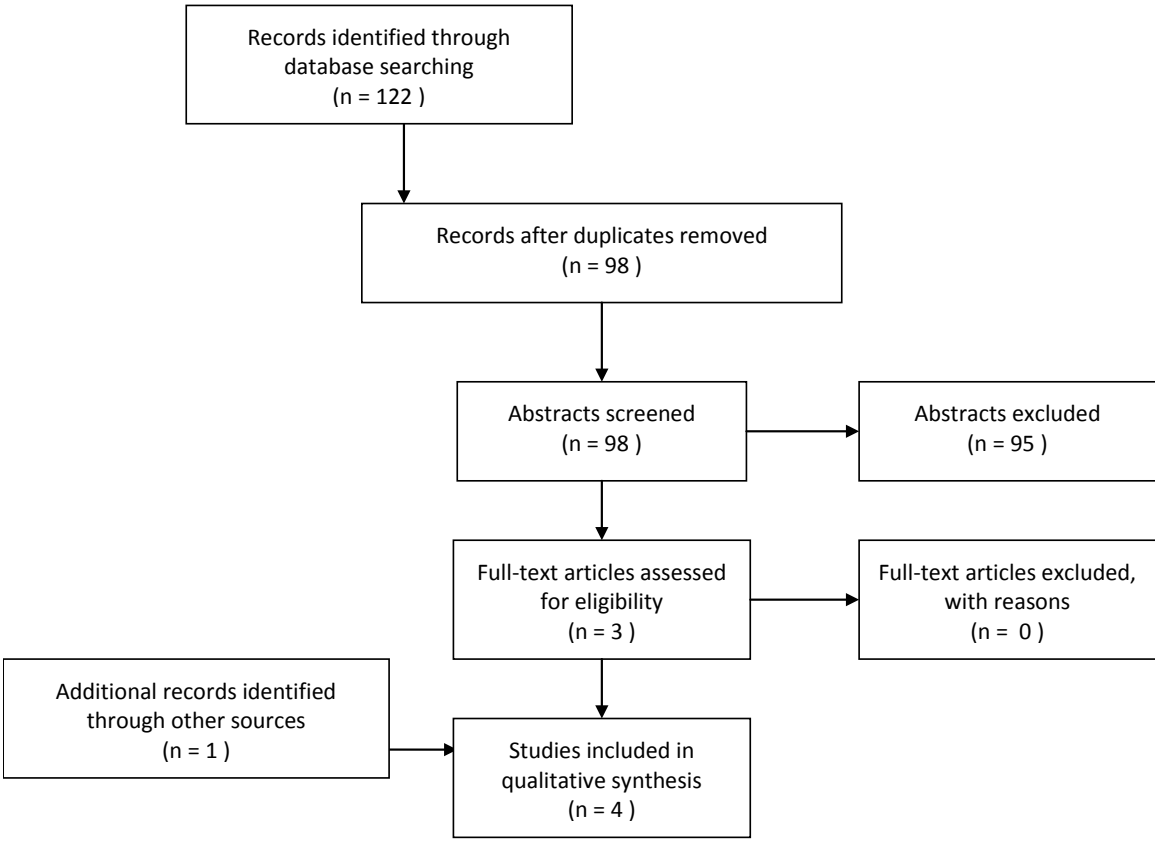
- Target population: Adults (≥18 years) with ITP (median/mean platelet counts < $30x10^9$/L at baseline) as a primary diagnosis. Studies including a proportion of patients with platelet count > $30x10^9$/L per microlitre at baseline were also included in the review providing some patients had a platelet count <$30x10^9$/L.
- Types of study: generic measures of utility and vignette utility studies.

The exclusion criteria were as follows:

- Studies not in the English language.
- References to studies reported as conference abstracts.
- Studies not reporting utility data.

Details of abstracts reviewed and studies excluded at each stage are presented in the PRISMA flow diagram in Figure B22.

Figure B22 PRISMA diagram for systematic review of utility studies



6.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

Three relevant utility studies were identified from this systematic review.[135;139;141] A fourth utility analysis – conducted to inform modeling in the intial eltrombopag submission to NICE[134] and updated in this submission – is also discussed.

Szende 2010[135]

The time-trade-off method was used by Szende et al (2010)[135] to elicit values for six health states pertaining to platelet level, bleeds and treatment related adverse events from 359 members of the UK general public (including Scotland and Wales). The survey was web based and the sample was considered to be comparable to the general UK population. The health state descriptions were based on individual patient data on the ITP-PAQ instrument collected during the romiplostim trials. Mean utility values ranged from 0.038 for intracranial haemorrhage to 0.863 for no bleed, sufficient platelets (

Table **B69**). This analysis also demonstrated that adverse events related to steroid treatment were associated with a decrement of 0.105 (no bleed, sufficient platelets vs. steroid treatment adverse events).

Table B69: Utility results for Szende 2010[135]

Results				
Component	**Mean**	**SD**	**Median**	**Estimated beta distribution**
No bleed, sufficient platelets	0.863	0.15	0.95	4.1, 1.2
Bleed, sufficient platelets	0.734	0.19	0.75	3.0, 1.1
No bleed, low platelets	0.841	0.19	0.90	4.8, 1.2
Bleed, low platelets	0.732	0.19	0.75	3.5, 1.1
Intracranial haemorrhage (2-6 months)	0.038	0.46	0.00	Not estimable
Steroid treatment adverse events	0.758	0.20	0.80	3.0, 1.1

Sanz 2011[139]

Sanz 2011[139] analysed EQ-5D data from the two 24-week placebo-controlled romiplostim trials. The romiplostim studies are discussed in detail in section 5.7. Patients enrolled in the romiplostim studies were asked to complete the EQ-5D at baseline (week 1) and weeks 5, 13 and 25. An assessment was made of the association between the improvement in health utility scores over the course of the 24 week trial and platelet response status. A similar assessment was undertaken to determine the impact of a bleeding related event on utility. The mean change from baseline to the last visit by treatment group was estimated using multiple linear regression models in responders versus nonresponders, and BRE versus non-BRE groups. Adjustment was made for age, gender, baseline EQ-5D scores and splenectomy status. A repeated measures regression model was also fit. Results are presented in Table B70 below.

Table B70 Health utilities of patients with chronic ITP (Sanz, 2011;[139] romiplostim studies)

Results				
Component	**Change from baseline EQ-5D**	**N**	**SE**	**P value**
Romiplostim treatment	0.05	76	0.02	0.015
Placebo treatment	-0.03	41	0.02	
Responders (romiplostim treatment)	0.03	37	0.02	0.834
Non-responders (romiplostim treatment)	0.03	39	0.02	
Had bleed related event (romiplostim treatment)	0.005	47	0.02	0.066
No bleed related event (romiplostim treatment)	0.06	29	0.03	

The Sanz 2011[139] analyses, although based on NICE's preferred methodology (administering the EQ-5D to patients and calculating tariff scores from this) does not provide information that can be utilized in the current model. The mean change in utility from baseline is provided according to patient categories (responder vs. non-responder and bleed related event vs. no bleed related event). As this approach does not take account of the fact that utility changes may be transitory (particularly those associated with bleeds) it is not appropriate for use in the present analysis. In addition to this, the failure to estimate the independent impact of platelet level and bleeds on utility would make it difficult to use the data in the model.

Iskedjian 2012[141]

Iskedjian 2012[141] used the time-trade-off method through an electronic survey in 821 adults (general public) from Canada to generate utility values for twelve health states (

Table B71). Participants were sampled through an opportunistic approach. These health states were defined based on response to watch and rescue treatment, bleeding status and presence of other adverse events. The descriptors in the health states were derived from the ITP-PAQ instrument and from the pivotal trials for romiplostim which used this instrument to assess the impact of treatment on quality of life. The time trade off approach elicited utilities on the basis of these health states. Mean utility values ranged from 0.633 for responders to romiplostim with no/mild bleed and no other adverse events to 0.476 for patients with significant bleeding. The results are presented below.

Table B71: Utility results for Iskedjian 2012[141]

Results					
Component	**Mean**	**Median**	**N**	**SD**	**95% CI**
Responders to romiplostim—No or Mild Dry Bleeding[13] (w/AEs other than bleeds)	0.633	0.681	265	0.282	0.599-0.667
Responders to W&R—No or Mild Dry Bleeding (w/AES other than bleeds)	0.623	0.664	266	0.274	0.590-0.656
Responders to romiplostim or W&R—Mild Other Bleeding/Moderate Dry Bleeding (w/out AEs other than bleeds)	0.620	0.633	263	0.269	0.586-0.652
Responders to romiplostim—Mild Other Bleeding/Moderate Dry Bleeding (w/AEs other than bleeds)	0.592	0.597	263	0.272	0.558-0.624
Responders to W&R—Mild Other Bleeding/Moderate Dry Bleeding (w/AEs other than bleeds)	0.628	0.667	267	0.276	0.595-0.661
Non-responders to romiplostim or W&R—No or Mild Dry Bleeding (w/out AEs other than bleeds)	0.588	0.567	268	0.276	0.555-0.621
Non-responders to romiplostim—No or Mild Dry Bleeding (w/AEs	0.605	0.631	269	0.267	0.573-0.637

[13] Dry bleeding was not formally defined in the paper, but appears to refer to "bruising or pinpoints, red dots, blood blisters"

other than bleeds)					
Non-responders to W&R—No or Mild Dry Bleeding (w/AEs other than bleeds)	0.579	0.553	259	0.275	0.544-0.612
Non-responders to romiplostim or W&R—Mild Other Bleeding/Moderate Dry Bleeding (w/out AEs other than bleeds)	0.545	0.500	273	0.279	0.512-0.578
Non-responders to romiplostim—Mild Other Bleeding/Moderate Dry Bleeding (w/AEs other than bleeds)	0.549	0.503	264	0.280	0.515-0.582
Non-responders to W&R—Mild Other Bleeding/Moderate Dry Bleeding (w/AEs other than bleeds)	0.517	0.497	266	0.289	0.481-0.551
Significant bleeding	0.476	0.489	267	0.271	0.443-0.508

The Iskedjian 2012 data are very specific to romiplostim with health state descriptions including a description of the injection and were elicited from the Canadian general population. As such it was not deemed appropriate to use these values in the economic model.

Eltrombopag submission to NICE, 2009[134]

Health related quality of life (HRQoL) was measured using the Short-Form 36-item instrument (SF-36v2). SF-36 assessments were collected as part of the clinical trial programme (RAISE and EXTEND study) at baseline, week 6, week 14 and on completion/withdrawal/follow-up of the study. At each SF-36 assessment, platelet count was also recorded giving rise to pairs of QoL and platelet count data. In the initial eltrombopag submission to NICE, SF-36 assessments pooled from RAISE and EXTEND and stratified by platelet count were mapped to the SF-6D using the Brazier *et al* algorithm (2002).[140] The resulting utility values are shown below in Table B72.

Table B72: Utility values from previous eltrombopag submission

Results					
Component	**Value**	**SD**	**SE**	**Min**	**Max**
Controlled platelet count (≥50Gi/L)	0.73	0.14	0.01	0.30	1.00
Uncontrolled platelet count (≥30Gi/L < 50Gi/L)	0.70	0.13	0.01	0.43	1.00
Controlled platelet count (≥30Gi/L)	0.73	0.14	0.01	0.30	1.00
Uncontrolled platelet count (< 30Gi/L)	0.69	0.13	0.01	0.30	1.00

For the current submission, a re-analysis of RAISE and EXTEND data (using a mixed model approach) was undertaken to relate utility to baseline utility, splenectomy status, platelet level (a binary variable of > and <50) and proximity to an outpatient bleed. This analysis and the results are described further in Appendix 17.

6.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Szende 2010[135] (used in the base case of the economic model in this submission) and the re-analysis of SF-6D mapping from SF-36 data in RAISE and EXTEND (used in a sensitivity analysis; section 6.6) assess similar health states. Although utility values in Szende 2010 are not split by splenectomy status, overall the utilities in the health states are comparable, ranging from 0.732 (for a patient with a bleed and low platelets) to 0.863 (for a patient with no bleed and sufficient platelets) in Szende 2010[135] and from 0.666 (for splenectomised patient with a bleed and low platelets) to 0.761 (for a non-splenectomised patient with no bleed and sufficient platelets).

The health states reported in Iskedjian 2012[141] were not equivalent to those reported in either Szende et al. (2010)[135] or in the re-analysis and mapping from the RAISE/EXTEND data. Iskedjian et al. (2012)[141] evaluated utilities based on the most common ITP symptoms and has, on balance, lower utilities across the states than those derived from mapping data from the RAISE and EXTEND studies. The inclusion of severe health states in the vignette studies led to a significantly lower base value, which may be a reason for this.

Sanz 2011[139] does not separate results by splenectomy status and reports a mean change from baseline EQ5D index scores. However, on the basis of a baseline EQ5D score of 0.8 in romiplostim treated patients and of 0.7 in patients in the placebo group, these results are not dissimilar to those in the other two studies; a range of utility values from 0.74 to 0.795.

Adverse events

6.4.8 Please describe how adverse events have an impact on HRQL.

Adverse events associated with ITP medication are a key determinant of HRQL in ITP patients. Withdrawal from treatment can be seen to temporarily improve HRQL in many cases (see section 6.4.1). The significance of the association between treatment related adverse events and utility was captured by the health states analysed by both Szende 2010[135] and Iskedjian 2012.[141] The Szende 2010[135] data have been used to capture the detrimental effect of steroid treatment on quality of life in the present analysis. In the absence of good quality data from the systematic review, utility values associated with other adverse events have been taken from TA221. Serious AEs are associated with the following implications; four week disutility of 0.1 for eltrombopag, romiplostim and rituximab; four week disutility of 0.4 for all other non–rescue treatments; four week disutility of 0.1 for rescue treatments. A blanket utility value of 0.1 is used for other AEs and again is applied for a four week period.

Disutilities associated with intracranial haemorrhage, gastrointestinal bleeds and other bleeds requiring inpatient treatment are derived from Szende 2010 for intracranial haemorrhage and Leontiadis 2007 for gastrointestinal bleed (GI).[135;142] Other bleeds requiring hospitalisation are assigned the same disutility as that for GI bleeds as they appeared similarly severe.

Quality-of-life data used in cost-effectiveness analysis

6.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.

Base case

The utility values utilized in the base case of the economic model are presented in the table below along with a description of the source of these data.

Table B73: Base case utilities

Health state	Mean	SE	Source
No bleed, sufficient platelets	0.863	0.0079	Szende 2010[135]
Bleed, sufficient platelets	0.734	0.0100	
No bleed, low platelets	0.841	0.0100	
Bleed, low platelets	0.732	0.0100	
Intracranial hemorrhage (2-6 months)	0.038	0.0243	
Steroid treatment AE	0.758	0.0106	
Gastrointestinal bleed	0.45	0.0561	Leontiadis, 2007[142]
Other bleed requiring inpatient treatment	0.45	0.0561	Assumption
4-week disutility associated with serious AEs (associated with eltrombopag, romiplostim and rituximab)	0.10	0.025	TA221[75]
4-week disutility associated with serious AEs (associated with all other non-rescue treatments)	0.40	0.1	
4-week disutility associated with serious AEs (associated with rescue treatments)	0.10	0.025	
Other AEs	0.10	0.025	

Alternative evaluation

In the alternative evaluation, in which input parameters were derived from a systematic review conducted by GSK and from post-hoc analyses of RAISE/EXTEND data, utilities are the same as in the base case analysis.

Sensitivity analyses

Utilities are varied in sensitivity analyses in the following way:

- One analysis explored the impact of using utilities derived from the mapping of SF-36 data from the RAISE and EXTEND trials to SF-6D and associated utilities (Table B74). Further detail is provided in Appendix 17.

Table B74: Utilities derived from RAISE/EXTEND used in sensitivity analysis

Health state	Splenectomised	Non-splenectomised
No bleed, sufficient platelets	0.737	0.761
Bleed, sufficient platelets	0.693	0.761
No bleed, low platelets	0.712	0.738
Bleed, low platelets	0.666	0.738
Intracranial hemorrhage (2-6 months)	As per base case	
Steroid treatment AE	As per base case	
Gastrointestinal bleed	As per base case	
Other bleed requiring inpatient treatment	As per base case	
4-week disutility associated with serious AEs (associated with eltrombopag, romiplostim and rituximab)	As per base case	
4-week disutility associated with serious AEs (associated with all other non-rescue treatments)	As per base case	
4-week disutility associated with serious AEs (associated with rescue treatments)	As per base case	
Other AEs	As per base case	

- In the scenario that incorporated all available input parameters from TA221 the utility values provided in the TA221 response to ACD (a combination of data from EQ-5D in the phase III trials and time trade-off utility values from a study in UK members of the public conducted by Amgen) are used (see section 6.6.2).

6.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[14]:

N/A

6.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

HRQL within the model is dependent not only upon platelet count and whether a patient is in a responder or non responder health state, but is also assumed to vary within states. This

[14] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

occurs as a result of bleeding events, adverse events (serious and other) and the detrimental impact of steroid treatment on HRQL. Estimates of the variance of utility values used across and within the health states were investigated through sensitivity analyses (see Appendix 17).

6.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

No health effects were excluded.

6.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Baseline quality of life was not assessed in the economic evaluation.

6.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

ITP is not a progressive disease therefore HRQL does not change over time. HRQL will vary as a result of treatment and the resulting platelet level, bleeding episodes and adverse events.

6.4.15 Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

Values have not been amended.

6.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

6.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

Costs considered in the model include acquisition costs for study medications, drug administration costs for those requiring infusions, costs of managing bleed events and long-term follow up costs. This could include inpatient, daypatient and outpatient treatments falling under a variety of HRG codes (NHS reference costs 2010/11). For the purpose of the economic evaluation drug costs were taken from the most recent edition of the BNF (63).[136] HRG codes and NHS reference costs (2010/11) were used to apply costs to ITP related hospitalisations and the cost of follow up.

6.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

Eltrombopag is a PbR excluded drug. NHS reference costs are appropriate for costing associated elements of care including administration costs, cost of treating bleed events and costs of long-term follow up.

Resource identification, measurement and valuation studies

6.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 9.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

A systematic search of the literature was carried out on the 6th February 2012 for costs associated with ITP. The following databases were searched: Embase, Medline and Medline-in-process, Econlit, HEED and NHS EED.

Full details of the search strategies are included in appendix 12.

Where appropriate, search strategies included controlled vocabulary terms applicable to the particular database. Free-text terms were used in all searches. The controlled vocabulary used was MeSH terms in Medline, Medline in process, and NHS EED; Emtree terms in Embase. The search strategies in Econlit and HEED included terms for ITP only as these databases contain references to economic literature only. The search strategies in Medline, Medline in process, Embase, NHS EED included terms for ITP and a filter to identify cost studies. All searches were limited to 2009 and onwards. The previous eltrombopag submission did not identify any cost studies from before 2009. This search should have retrieved all papers relevant to this section and was therefore not repeated. The search strategy that was employed in section 6.1.1 was used here again, as any study reporting cost data would be picked up by the same filter. Alternative criteria for the selection of studies were applied for this review.

The inclusion criteria were as follows:

- Target population: Adults (≥18 years) with ITP (median/mean platelet counts < 30 x 10^9/L at baseline) as a primary diagnosis. A proportion of patients with platelet count > 30 x 10^9/L at baseline were also included in the review providing the study also included some patients with a platelet count <30 x 10^9/L.
- Types of study: Any studies reporting UK costs associated with ITP health states or toxicities.

The exclusion criteria were as follows:

- Studies not in the English language.
- References to studies reported as conference abstracts.

No relevant cost studies were identified by the systematic review. Details of abstracts reviewed and studies excluded at each stage are presented in the PRISMA flow diagram in Figure B23.

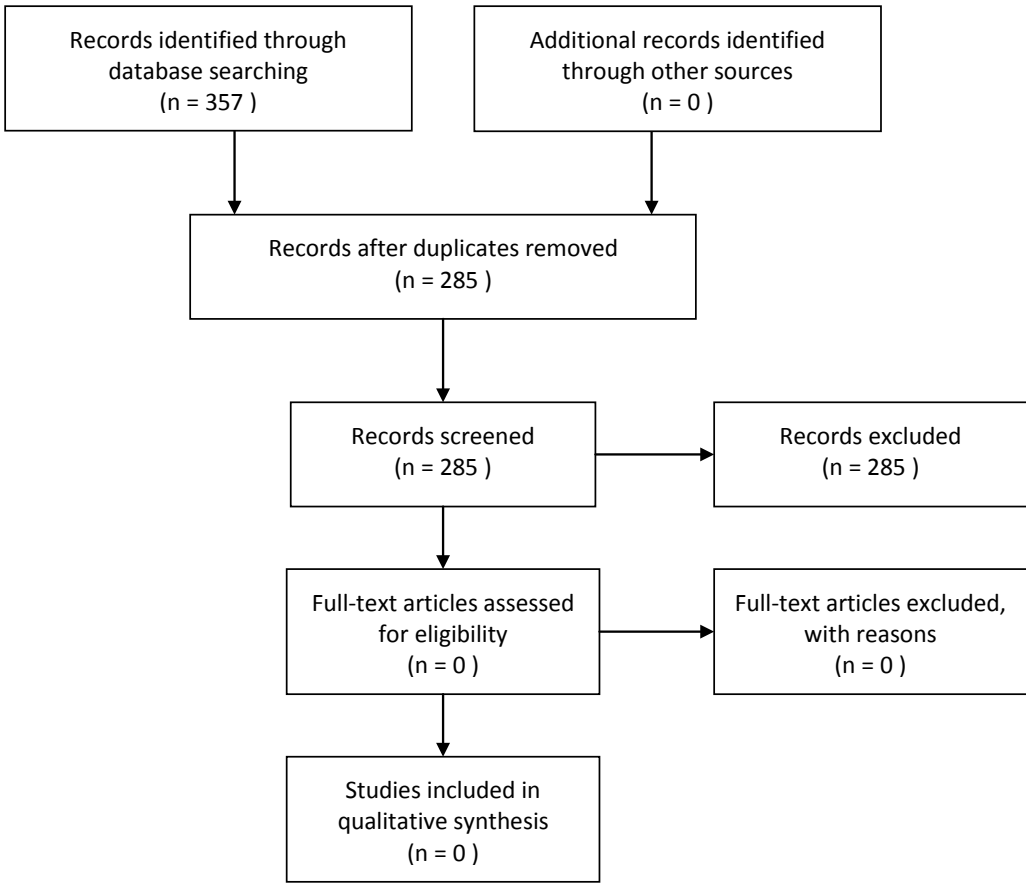


Figure B23: PRISMA diagram for systematic review of costs

In the absence of data from peer-reviewed published literature, the best available unpublished sources, supplemented with assumption as necessary, were used to estimate the relevant costs for this economic model.

6.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[15]:

See section 6.3.5.

Intervention and comparators' costs

6.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

[15] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

6.5.6 All drug costs were taken from the most recent edition of British National Formulary (BNF 63 [136]). A patient access scheme has been incorporated into the model that discounts eltrombopag at [redacted] and romiplostim at [redacted] The drug costs used are presented in Table B75.

Table B75: Acquisition costs used in economic modelling (BNF 63)[136]

Drug	Cost per pack	Size (mg)
Eltrombopag	£770.00	700 (28 x 25mg)
Romiplostim	£482.00	0.25
Rituximab	£174.63	100
Azathioprine	£5.04	1,400
Mycophenolate mofetil	£35.00	25,000
Ciclosporin	£13.80	750
Dapsone	£54.56	2,800
Danazol	£16.38	6,000
Cyclophosphamide	£20.20	5,000
Vincristine	£13.47	1
Vinblastine	£13.09	10
Rescue – IVIg	£45.00	1,000
Rescue – Anti-D	£46.50	0.30
Rescue – IV steroid	£5.73	25

Administration costs

Administration and acquisition costs do not change between the base case and the alternative evaluation aside from the incorporate of platelet transfusions as rescue therapy in the alternative evaluation.

Drug administration costs were estimated from NHS reference costs 2010/2011. Administration of romiplostim, vincristine and vinblastine are assumed to fall under the simple chemotherapy cost code SB12Z (weighted average cost of £204.81 per infusion); rituximab and IV steroids under the complex chemotherapy, including prolonged infusional treatment code SB14Z (weighted average cost of £330.59). These codes reflect HRG codes for delivery of chemotherapy.

IVIg and Anti-D are assumed to fall under code XD34Z (Immunoglobulins band 1, weighted

average cost of £1,235.34 per infusion).

The alternative evaluation which relies on data from the systematic review conducted by GSK and on data from RAISE/EXTEND also incorporates platelet transfusions as rescue therapy. In the model, platelet transfusions were assumed to comprise a cost of blood transfusion (weighted average cost of £57.72, code 821 blood transfusion) and the cost of two units of platelets (2 x £230.393)[16]. A sensitivity analysis which incorporates all data from TA221 (where possible) assumes a follow up cost of £262 per 4 week cycle.

For the administration of romiplostim, it was assumed that patients who receive the same dose for three consecutive weeks can receive home administration. This criterion was the same applied in the open label extension study for romiplostim.[61] Home administration is assumed to be associated with no administration costs. The proportion of patients who were eligible to receive home administration was modelled based on figures presented by Kuter *et al* at the 52nd ASH conference in 2010.[69] The abstract stated that 82% of patients initiated home administration and out of these 88.3% continued until the end of the study. This equates to 211 (72.3%) of 292 patients that entered the study persisting with home administration. We therefore assume that no patient has home administration for the first cycle (4 weeks) and then from cycle 2 onwards 72.3% of patients have home administration. The use of home administration is thought to be variable in practice therefore a sensitivity analysis assuming no home administration has also been conducted where a weekly visit has been assumed.

The administration costs assumed in the base case are reflected in Table B76 below:

Table B76: Administration costs

Drug	Administration code	Source
Romiplostim	SB12Z (simple chemo, first attendance)	NHS reference costs
Rituximab	SB14Z (complex chemo w prolonged infusion, first attendance)	NHS reference costs
Vincristine	SB12Z (simple chemo, first attendance)	NHS reference costs
Vinblastine	SB12Z (simple chemo, first attendance)	NHS reference costs
Rescue – IVIg	XD34Z (Immunoglobulins band 1)	NHS reference costs
Rescue – Anti-D	XD34Z (Immunoglobulins band 1)	NHS reference costs
Rescue – IV steroid	SB14Z (complex chemo w prolonged infusion, first attendance)	NHS reference costs

Oral treatments, azathioprine, mycophenolate mofetil, ciclosporin, dapsone, danazol and cyclophosphamide are assumed to have no administration costs.

[16] Cost of platelets taken from NHS Blood and Transplant, NATIONAL COMMISSIONING OF BLOOD, COMPONENTS AND SPECIALIST SERVICES 2010/11, 26th November 2009. Available from: http://www.nhsbt.nhs.uk/downloads/board_papers/nov09/ncg_09_89.pdf

Health-state costs

6.5.7 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 6.2.4.

Further to treatment costs, costs were assumed to be incurred as a result of the treatment of bleeds and the costs of follow up.

The cost per bleed type was taken from the latest edition of the NHS reference costs. The relevant HRG codes and the associated NHS reference costs for both gastrointestinal bleed and intracranial haemorrhage are displayed in Table B77. The cost of other bleeds requiring hospitalisation was assumed to be equal to that associated with gastrointestinal bleed.

Table B77: Cost of bleeds

Bleed type	HRG code	NHS Ref costs
Day case bleed	SA08F Other Haematological or Splenic Disorders without CC – day case	£302.81
Gastrointestinal bleed	FZ38 Gastrointestinal haemorrhage, unspecified	Inpatient £1,553 (weighted average over HRG codes FZ38D, FZ38E and FZ38F)
Intracranial haemorrhage	Intracranial haemorrhage (non-traumatic), unspecified	Inpatient £3,451 (weighted average over HRG codes AA23A and AA23B)
Other bleed requiring hospitalization	Assumed equal to FZ38.	Inpatient £1,553

Cost of follow-up

Patients were assumed to receive one haematologist consultation (HRG 303), and two laboratory tests, full blood count and biochemistry assessment, each month during treatment. The cost of the blood test is assumed to be captured by the indicative tariff 2010/11 for haematological tests (DAP823) and the biochemistry tarrif (DAP841) is assumed to capture the costs of liver function tests. These are summarised in Table B78.

Table B78: Cost of follow-up

Item	HRG code	NHS Ref costs
Haematologist consultation	303 Clinical Haematology, Consultant led: First Attendance Non-Admitted Face to Face	£147.53
Blood test	DAP823 Haematology [Excluding Anti-Coagulant Services]	£3.00
Biochemistry	DAP841 Biochemistry	£1.00

Adverse-event costs

6.5.8 Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

The costs of bleeding are incorporated into the economic model (see section 6.5.8) although the model does not incorporate the costs of treating other adverse events associated with treatment. Additionally, the long-term adverse events associated with treatments such as corticosteroids and splenectomy are not accounted for in the model. This may underestimate the true cost of the non-TPO RA pathway.

Miscellaneous costs

6.5.9 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

None. No PSS costs were identified.

6.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

The point at which TPO-RAs were positioned in the treatment pathway was explored through sensitivity analyses. These are outlined below.

6.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

One-way sensitivity analyses

Table B79. Deterministic sensitivity analyses

Deterministic sensitivity analyses		Rationale
Treatment pathway	TPO-RAs received prior to rituximab	This is consistent with TA221.
	TPO-RAs as last active treatment (compared to no active treatment)	Clinical opinion suggests that TPO-RAs may sometimes be used in this setting.
	Rituximab replaced by TPO-RA in sequence	This allows a comparison of TPO-RAs against a pathway incorporating rituximab.
Efficacy parameters	Odds ratio of 1.0 for TPO-RA comparison. Response rate for TPO-RAs equal to the overall response (post hoc analysis of overall response estimated from RAISE)	This provides a more conservative estimate of the efficacy of TPO-RAs.
	Overall response rate used for eltrombopag (post hoc analysis of RAISE). Odds ratio from indirect comparison of overall response used to calculate response rate for romiploatim.	This takes into account the available comparative evidence for TPO-RAs by using the point estimates (statistically insignificant) from an indirect comparison of overall response.
	Time on treatment, responders, log-logistic	These analyses explore the impact of alteranative estimates of time on treatment (see appendix 15 for details)
	Time on treatment, responders, Gamma	
	Time on treatment, all patients. Gompertz	
	Time on treatment, all patients, log-logistic	
	Time on treatment, all patients, Weibull	
	Mortality modelled via platelet level rather than bleeds	This is provided as an alternative to modelling mortality associated with hospitalised bleeds.
Rescue rates for patients with platelets <50 x10^9 (per month)	RAISE/EXTEND rate -25%	The base case uses rescue rates from TA221. These analyses explore the impact of higher (TA221 +25%) and lower (derived from RAISE/EXTEND) rescue rates.
	RAISE/EXTEND rate	
	Mid point RAISE/EXTEND and TA221	
	TA221 rate	
	TA221 rate+25%	
Proportions of rescue treatments	Proportion IVIg + 25%	These analyses explore the impact of changing the proportion of rescue treatment that comprises IVIg.
	Proportion IVIg – 25%	
Rate of serious bleeds for patients with <50 x 10^9(per month)	RAISE/EXTEND rate -25%	The base case uses bleeding rates from TA221. These analyses explore the impact of higher (TA221 +25%) and lower (derived from RAISE/EXTEND) rescue rates.
	RAISE/EXTEND rate	
	Mid point RAISE/EXTEND and TA221	
	TA221	
	TA221 +25%	

Costs	All patients receive romiplostim as outpatient visit	The base case assumes patients can self administer at home. Clinical opinion suggests that this is not always the case therefore the impact of incorporating a weekly outpatient visit for romiplostim is explored.
	No PAS for eltrombopag	[redacted]
	Romiplostim dose from Bussel 2009	The base case models the romiplostim dose according to data reported for the Kuter trials. In this sensitivity analysis the extension trial is used to model the romiplostim dose.
Decision maker parameters	Discount rate = 0%	
	Discount rate= 6%	
	Time horizon 6 months	
	Time horizon 5 years	
	Time horizon 10 years	
	Time horizon 20 years	
Structural	Bleed risk in final non-responder state same as other non-responder states	The base case assumes that once patients have exhausted the treatments in the pathway and enter a final non responder state the risk of bleeding doubles. This sensitivity analysis explores the impact of not making this assumption.

Multi-way sensitivity analyses

In addition to the alternative evaluation that is outlined in Section 6.2.2, a scenario analysis was conducted that aims to more fully reflect the assumptions in TA221.[75] This was conducted to understand the differences between the base case results and those reported in TA221 and to further explore the sensitivities of the model. Although details for some parameters were not available and it was not always clear how some parameters had been calculated or incorporated, the following modifications to the base case were made.

- Romiplostim dosing: "realistic scenario" from the manufacturers PAS submission (0.99 for non-splenectomised and 1.35 for splenectomised patients [143]) was used to obtain the number of required vials. These vial numbers reflect the number of vials required assuming availability of a 100mcg vial size. [redacted]
- Response rate for both TPO-RAs are set as per the TA221 PAS submission i.e. excluding patients responding once dosed beyond license [143]. The response rates used are 76% and 85% for splenectomised and non-splenectomised patients respectively.
- Rescue rates were calibrated to produce 24 week rescue rates of 1.86 for non-splenectomised and 2.67 for splenectomised patients [75] when the treatment pathway is set to include no maintenance treatments.
- TPO-RAs were assumed to be administered prior to rituximab in the sequence, and

59% of patients receive rituximab [143]

- Utilities are based on pooled EQ-5D and vignette utility data as per the romiplostim PAS submission [143]. The values used are provided as Table B80.

Table B80: Utility values used in TA221 PAS submission

Health state	Mean utility
No bleed, sufficient platelets	0.84
Bleed, sufficient platelets	0.73
No bleed, low platelets	0.80
Bleed, low platelets	0.73
Intracranial hemorrhage (2-6 months)	0.04
Gastrointestinal bleed	0.54
Other bleed requiring inpatient	0.54

- Time on treatment, follows an exponential distribution with mean time equal to 7.07 for non-splenectomised and 6.32 for splenectomised patients as per TA221 [75]
- Administration costs were set to £262 per cycle for all treatments, no additional cost associated with romiplostim administration were incorporated [75]

6.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 6.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

Probabilistic sensitivity analyses were conducted by simultaneously sampling from estimated probability distributions of model parameters to obtain 1,000 sets of model input estimates.

A table of the distributions used in the probabilistic sensitivity analysis is presented as Table B81.

Table B81: Parameters and distributions used in probabilistic sensitivity analysis (Base case and alternative evaluation)

Parameter	Distribution and parameterization
Probability of receiving each treatment	Beta, parameterised using parameter estimates from TA221 [75]
Response rates	TPO-RA: Beta, event rates and sample sizes obtained from RAISE IPD. For odds ratio comparing romiplostim and eltrombopag s.e. of log odds ratio = 1.0 to reflect uncertainty regarding relative efficacy of treatments. Non TPO-RA: beta distribution, for base case parameters taken from TA221 [75]. For alternative evaluation n taken from appropriate study.
Time to response	Gamma, assume s.e. = 0.25*mean
Time on treatment	TPO-RA: multivariate normal distribution assumed for parameters of parametric distributions. Variance/covariance matrices are provided in Appendix 15. Non TPO-RA: Gamma, assume s.e. = 0.25*mean
Rescue rates	For base case beta distribution with parameters taken from TA221 [75]. For alternative evaluation gamma distributions used assuming variance equal to mean.
Distribution of rescue types	Dirichlet: for base case values assumed to be taken from sample of 167 physicians (as per TA221 physician survey [75]); for alternative evaluation events taken directly from IPD for RAISE/EXTEND
Bleed rates	Base case: beta distribution with parameters from TA221 used. alternative evaluation: Gamma, assumed variance equal to mean
Proportion of patients experiencing each bleed type	Dirichlet, directly parameterised using event counts
Rates of mortality conditional upon bleed	Beta: α and β derived from events and sample size in Danese 2008 [17]
Utilities – health states and bleeds	Log-normal distribution use to model decrement from full health, parameterised using mean and standard errors from Szende 2010[135] and Leontiadis 2007 [142]
Adverse event rates	Beta: parameters obtained from TA221 [75]
Adverse event disutilities	Log-normal distribution use to model decrement, s.e. assumed equal to 0.25*mean
Romiplostim and eltrombopag mean doses	Log-normal, mean and standard errors available from RAISE/EXTEND IPD for eltrombopag, and Kuter 2008 [144] and Bussel 2009[61] for romiplostim
Proportion of patients receiving romiplostim as home administration	Beta: α and β derived from events and sample size in Kuter 2010[60]
Cost of bleeds, long-term follow up and treatment administration	Gamma used for unit costs, s.e. assumed equal to 0.25*mean. Dirichlet used for distribution of activity, directly parameterised using NHS reference cost activity rates.

6.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

6.7.1 For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

6.7.2 Most of the outcomes highlighted in the decision problem comprise model inputs, which have been taken from clinical trial data. Relevant outcomes for comparison with trial data are considered to be IVIg administrations, serious bleeds, mortality and patients on treatment.

Table B82 and Table B33 compare modelled outcomes over a 24 week time horizon to those reported in the pivotal trials for eltrombopag and romiplosti

Table B82: Summary of model results compared with clinical data for splenectomised patients (NOTE: 6 month clinical data compared to 24 week model predictions)+

Outcome	Eltrombopag		Romiplostim		Non TPO-RA pathway			Source - RAISE	Source – Kuter
	Clinical trial result (RAISE)	Model result	Clinical trial result (Kuter)	Model result	Clinical trial result (placebo, RAISE)	Clinical trial result (placebo, Kuter 2008)	Model result		
IVIg events per person	0.68*	0.86	NR	0.86	1.25*	2.67	2.00	GSK Data on file Table 6.708	TA221 manufacturer submission
Serious bleeds (% pts. experiencing CTCAE >=G3)	<1%	5%	6%	5%	7%	10%	13%	CSR p123	FDA advisory committee briefing document
Probability of death	0.0%	0.4%	0.0%	0.4%	1.6%	4.9%	0.7%	CSR p118	Kuter 2008 (note: during study, 2 additional deaths post completion)
Patients on treatment	83.0%	67.1%	NA	67.1%	NA	NA	NA	CSR p53 [received 26 weeks of study medication and completed the 1-, 2-, and 4-week follow-up visits]	Not available

+Note data not always available by splenectomy status; * Usage of IVIg in developed countries

Table B83: Summary of model results compared with clinical data for non splenectomised patients (NOTE: 6 month clinical data compared to 24 week model predictions)+

Outcome	Eltrombopag		Romiplostim		Non TPO-RA pathway			Source - RAISE	Source – Kuter
	Clinical trial result (RAISE)	Model result	Clinical trial result (Kuter)	Model result	Clinical trial result (placebo, RAISE)	Clinical trial result (placebo, Kuter 2008)	Model result		
IVIg events per person	0.41*	0.32	NR	0.32	0.47*	1.86	0.92	GSK Data on file Table 6.708	TA221 manufacturer submission
Serious bleeds (% pts. experiencing CTCAE >=G3)	<1%	6%	6%	6%	7%	10%	19%	CSR p123	FDA advisory committee briefing document
Probability of death	0.0%	0.4%	0.0%	0.4%	1.6%	4.9%	1.0%	CSR p118	Kuter 2008 (note: during study, 2 additional deaths post completion)
Patients on treatment	83.0%	75.2%	NA	75.2%	NA	NA	NA	CSR p53 [received 26 weeks of study medication and completed the 1-, 2-, and 4-week follow-up visits]	Not available
+Note data not always available by splenectomy status; * Usage of IVIg in developed countries									

The model predicts higher rescue rates in the eltrombopag arm for splenectomised patients than observed in the RAISE trial, and a higher rate than observed in the placebo arm of RAISE. This is due to the use of the TA221 data regarding rescue use in the base case. Compared to the Kuter 2008[60] placebo arm data the model predicts a lower rate of rescue use for the non TPO-RA pathway. This is due to the use of an active comparator arm in the model. For non-splenectomised patients the rate of rescue in the eltrombopag arm is slightly lower than observed in the trial; however this is probably due to the low event rates during the trial.

The rate of serious bleeds was, accounting for sample size, similar in the TPO-RA arms of the model compared to the trials. The model predicted a rate of 0.05-0.06 for both treatments, compared to <1% and 6% in the eltrombopag arm of RAISE and the romiplostim arm of Kuter 2008 respectively. Results for the non-TPO RA pathway showed a higher rate of bleeds (0.13-0.19) than observed in the trials (7% and 10% in the placebo arms of RAISE and Kuter 2008). However this is likely due to the fact that the model estimates refer to bleed rates, whereas the clinical data reports proportions of patients experiencing one or more serious bleeds. The latter is likely to underestimate bleed rates due to the likelihood of patients experiencing multiple events. The number of serious bleeds is predicted to be higher in non-splenectomised patients. This is due to the lower rate of rescue in this group, which puts more patients at risk of bleed.

The probability of death was similar in the TPO-RA arms of the trials compared to the model predictions. The predicted proportion of patients dying on the non TPO-RA pathway was 0.7-1.0% compared to 4.9% in the placebo arm of Kuter 2008 and 1.6% in the placebo arm of RAISE. This is likely to be attributable to low event numbers (and the associated uncertainty) and the use of an active TPO-RA pathway as the comparator. The model may also underestimate mortality due to the use of US data to estimate the probability of death conditional upon hospitalisation. If in the locations in which the RAISE and Kuter 2008 trials were conducted hospitalisation was likely to occur only for more serious events, then the mortality rate associated with bleeds requiring hospitalisation may be underestimated. In addition, the exclusion of emergency room hospitalisations may also have reduced the rate of death.

Withdrawal rates in the TPO-RAs are predicted to be higher by the model than observed in the trials. This reflects the fact that all non-responders were taken off treatment within one cycle of treatment in the model. This did not occur in the trial, where investigators were presumably less likely to discontinue study medication.

Overall the model predictions can be considered broadly comparable to clinical trial results.

6.7.3 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Table B84 and Table B85 below show the proportion of the model cohort occupying each aggregated health state over time for each treatment in the intervention and comparator arms. The individual health states presented are:

- TTR: Time to response
- LTR: Long term response
- LTNR: Long term non-response

Time to response health states represent the four tunnel states used to model time to response and are represented in the Markov trace below along with the proportion of patients in the long-term responder state. Time to response and the long term responder states are aggregated as patients within these states will be subject to the same assumptions.

These traces demonstrate that patients receiving a treatment pathway incorporating a TPO-RA spend more time in a responder state (platelets $\geq 50x10^9$/L) than those receiving a non TPO-RA pathway.

Table B84: Markov traces - splenectomised

Eltrombopag

Time (years)	Time Weeks	All cause mortality	ITP related mortality	Eltrombopag		Azathioprine		Mycophenolate mofetil		Ciclosporin		Danazol		Dapsone		Cyclophosphamide		Vinblastine		Vincristine	
				TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR
1 year	52	0%	0%	57%	3%	13%	2%	4%	1%	0%	0%	1%	0%	3%	1%	0%	0%	0%	0%	0%	12%
2 years	104	0%	1%	45%	2%	12%	2%	3%	1%	1%	0%	1%	0%	5%	1%	0%	0%	0%	0%	0%	25%
3 years	156	1%	2%	37%	1%	9%	1%	2%	1%	1%	0%	2%	0%	5%	1%	0%	0%	0%	0%	0%	36%
4 years	208	1%	3%	32%	1%	7%	1%	2%	1%	0%	0%	2%	0%	4%	1%	0%	0%	0%	0%	0%	45%
5 years	260	1%	5%	28%	1%	5%	1%	1%	0%	0%	0%	2%	0%	4%	1%	0%	0%	0%	0%	0%	51%
10 years	520	3%	13%	16%	0%	2%	0%	0%	0%	0%	0%	2%	0%	1%	0%	0%	0%	0%	0%	0%	62%
20 years	1040	9%	28%	8%	0%	0%	0%	0%	0%	0%	0%	1%	0%	0%	0%	0%	0%	0%	0%	0%	53%
25 years	1300	14%	35%	5%	0%	0%	0%	0%	0%	0%	0%	1%	0%	0%	0%	0%	0%	0%	0%	0%	44%
30 years	1560	20%	40%	4%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	35%
35 years	1820	29%	44%	2%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	24%
50 years	2600	50%	48%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1%

Romiplostim

Time (years)	Time Weeks	All cause mortality	ITP related mortality	Romiplostim		Azathioprine		Mycophenolate mofetil		Ciclosporin		Danazol		Dapsone		Cyclophosphamide		Vinblastine		Vincristine	
				TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR
1 year	52	0%	0%	57%	3%	13%	2%	4%	1%	0%	0%	1%	0%	3%	1%	0%	0%	0%	0%	0%	12 %
2 years	104	0%	1%	45%	2%	12%	2%	3%	1%	1%	0%	1%	0%	5%	1%	0%	0%	0%	0%	0%	25 %
3 years	156	1%	2%	37%	1%	9%	1%	2%	1%	1%	0%	2%	0%	5%	1%	0%	0%	0%	0%	0%	36 %
4 years	208	1%	3%	32%	1%	7%	1%	2%	1%	0%	0%	2%	0%	4%	1%	0%	0%	0%	0%	0%	45 %
5 years	260	1%	5%	28%	1%	5%	1%	1%	0%	0%	0%	2%	0%	4%	1%	0%	0%	0%	0%	0%	51 %
10 years	520	3%	13%	16%	0%	2%	0%	0%	0%	0%	0%	2%	0%	1%	0%	0%	0%	0%	0%	0%	62 %
20 years	1040	9%	28%	8%	0%	0%	0%	0%	0%	0%	0%	1%	0%	0%	0%	0%	0%	0%	0%	0%	53 %
25 years	1300	14%	35%	5%	0%	0%	0%	0%	0%	0%	0%	1%	0%	0%	0%	0%	0%	0%	0%	0%	44 %
30 years	1560	20%	40%	4%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	35 %
35 years	1820	29%	44%	2%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	24 %
50 years	2600	50%	48%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1%

Non TPO-RA pathway

Time (years)	Time Weeks	All cause mortality	ITP related mortality	Azathioprine		Mycophenolate mofetil		Ciclosporin		Danazol		Dapsone		Cyclophosphamide		Vinblastine		Vincristine	
				TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR
1 year	52	0%	1%	24%	3%	7%	3%	1%	0%	3%	0%	10%	3%	0%	0%	0%	0%	0%	43%
2 years	104	0%	3%	14%	2%	3%	1%	1%	0%	3%	0%	9%	2%	1%	0%	0%	0%	0%	63%
3 years	156	1%	5%	8%	1%	1%	1%	1%	0%	3%	0%	6%	1%	0%	0%	0%	0%	0%	72%
4 years	208	1%	7%	4%	0%	1%	0%	0%	0%	3%	0%	4%	1%	0%	0%	0%	0%	0%	77%
5 years	260	1%	9%	2%	0%	0%	0%	0%	0%	3%	0%	3%	0%	0%	0%	0%	0%	0%	80%
10 years	520	3%	19%	0%	0%	0%	0%	0%	0%	2%	0%	0%	0%	0%	0%	0%	0%	0%	75%
20 years	1040	8%	37%	0%	0%	0%	0%	0%	0%	1%	0%	0%	0%	0%	0%	0%	0%	0%	54%
25 years	1300	13%	43%	0%	0%	0%	0%	0%	0%	1%	0%	0%	0%	0%	0%	0%	0%	0%	44%
30 years	1560	18%	48%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	33%
35 years	1820	25%	52%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	22%
50 years	2600	43%	56%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1%

Table B85: Markov traces - non splenectomised

Eltrombopag trace

Time (years)	Time Weeks	All cause mortality	ITP related mortality	Eltrombopag		Azathioprine		Mycophenolate mofetil		Ciclosporin		Danazol		Dapsone		Cyclophosphamide		Vinblastine		Vincristine	
				TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR
1 year	52	0%	1%	68%	2%	8%	1%	4%	1%	0%	0%	1%	0%	3%	1%	0%	0%	0%	0%	0%	9%
2 years	104	0%	1%	59%	1%	7%	1%	2%	1%	0%	0%	1%	0%	4%	1%	0%	0%	0%	0%	0%	20%
3 years	156	1%	2%	51%	1%	6%	1%	2%	1%	0%	0%	1%	0%	4%	1%	0%	0%	0%	0%	0%	28%
4 years	208	1%	4%	46%	1%	5%	1%	2%	0%	0%	0%	1%	0%	4%	1%	0%	0%	0%	0%	0%	35%
5 years	260	1%	5%	41%	1%	4%	1%	1%	0%	0%	0%	1%	0%	3%	1%	0%	0%	0%	0%	0%	40%
10 years	520	3%	14%	27%	0%	2%	0%	0%	0%	0%	0%	1%	0%	1%	0%	0%	0%	0%	0%	0%	49%
20 years	1040	9%	32%	15%	0%	1%	0%	0%	0%	0%	0%	1%	0%	0%	0%	0%	0%	0%	0%	0%	42%
25 years	1300	13%	40%	11%	0%	0%	0%	0%	0%	0%	0%	1%	0%	0%	0%	0%	0%	0%	0%	0%	34%
30 years	1560	19%	46%	8%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	26%
35 years	1820	27%	50%	5%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	18%
50 years	2600	45%	54%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1%

Romiplostim trace

Time (years)	Time Weeks	All cause mortality	ITP related mortality	Romiplostim		Azathioprine		Mycophenolate mofetil		Ciclosporin		Danazol		Dapsone		Cyclophosphamide		Vinblastine		Vincristine	
				TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR
1 year	52	0%	1%	68%	2%	8%	1%	4%	1%	0%	0%	1%	0%	3%	1%	0%	0%	0%	0%	0%	9%
2 years	104	0%	1%	59%	1%	7%	1%	2%	1%	0%	0%	1%	0%	4%	1%	0%	0%	0%	0%	0%	20%
3 years	156	1%	2%	51%	1%	6%	1%	2%	1%	0%	0%	1%	0%	4%	1%	0%	0%	0%	0%	0%	28%
4 years	208	1%	4%	46%	1%	5%	1%	2%	0%	0%	0%	1%	0%	4%	1%	0%	0%	0%	0%	0%	35%
5 years	260	1%	5%	41%	1%	4%	1%	1%	0%	0%	0%	1%	0%	3%	1%	0%	0%	0%	0%	0%	40%
10 years	520	3%	14%	27%	0%	2%	0%	0%	0%	0%	0%	1%	0%	1%	0%	0%	0%	0%	0%	0%	49%
20 years	1040	9%	32%	15%	0%	1%	0%	0%	0%	0%	0%	1%	0%	0%	0%	0%	0%	0%	0%	0%	42%
25 years	1300	13%	40%	11%	0%	0%	0%	0%	0%	0%	0%	1%	0%	0%	0%	0%	0%	0%	0%	0%	34%
30 years	1560	19%	46%	8%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	26%
35 years	1820	27%	50%	5%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	18%
50 years	2600	45%	54%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1%

Non TPO-RA trace

Time (years)	Time Weeks	All cause mortality	ITP related mortality	Azathioprine		Mycophenolate mofetil		Ciclosporin		Danazol		Dapsone		Cyclophosphamide		Vinblastine		Vincristine	
				TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR	TTR/LTR	LT NR
1 year	52	0%	2%	19%	2%	8%	3%	1%	0%	2%	0%	11%	2%	1%	0%	0%	0%	0%	46%
2 years	104	0%	4%	11%	1%	3%	1%	1%	0%	3%	0%	10%	1%	1%	0%	0%	0%	0%	65%
3 years	156	1%	7%	6%	1%	1%	0%	0%	0%	2%	0%	7%	1%	1%	0%	0%	0%	0%	73%
4 years	208	1%	10%	3%	0%	1%	0%	0%	0%	2%	0%	4%	1%	0%	0%	0%	0%	0%	76%
5 years	260	1%	13%	2%	0%	0%	0%	0%	0%	2%	0%	3%	0%	0%	0%	0%	0%	0%	77%
10 years	520	3%	27%	0%	0%	0%	0%	0%	0%	1%	0%	0%	0%	0%	0%	0%	0%	0%	68%
20 years	1040	7%	48%	0%	0%	0%	0%	0%	0%	1%	0%	0%	0%	0%	0%	0%	0%	0%	44%
25 years	1300	11%	56%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	33%
30 years	1560	15%	61%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	24%
35 years	1820	20%	65%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	15%
50 years	2600	31%	68%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1%

6.7.4 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

QALYs are accrued according to the proportion of patients that are in a responder or non responder health state over time (i.e. have not exited the model due to all cause or ITP related mortality). This is adjusted for the disutility that patients experience whilst residing in these health states.

6.7.5 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

A summary of model outputs by clinical outcomes is provided as Table B86 for splenectomised patients and Table B87 for non-splenectomised patients. Further exploration of these results, as required by the NICE template is available in the Excel model.

Table B86: Model outputs by clinical outcomes (discounted), splenectomised patients

Outcome	Eltrombopag		Romiplostom		Non TPO-RA pathway	
	LY	QALY	LY	QALY	LY	QALY
On TPO-RA	3.90	3.37	3.90	3.37	0.00	0.00
On non TPO-RA	1.44	1.24	1.44	1.24	1.72	1.48
Off treatment (between active treatments)	0.38	0.32	0.38	0.32	0.27	0.23
Off treatment (exhausted active treatments)	9.83	8.37	9.83	8.37	12.36	10.52
Bleeds	0.00	-0.87	0.00	-0.87	0.00	-1.03
AEs	0.00	-0.21	0.00	-0.21	0.00	-0.25
Total	15.56	12.22	15.56	12.22	14.35	10.95
LY, life years; QALY, quality-adjusted life year						

Table B87: Model outputs by clinical outcomes (discounted), non-splenectomised patients

Outcome	Eltrombopag		Romiplostom		Non TPO-RA pathway	
	LY	QALY	LY	QALY	LY	QALY
On TPO-RA	5.83	5.03	5.83	5.03	0.00	0.00
On non TPO-RA	1.17	1.01	1.17	1.01	1.56	1.34
Off treatment (between active treatments)	0.31	0.26	0.31	0.26	0.25	0.21
Off treatment (exhausted active treatments)	7.72	6.53	7.72	6.53	10.98	9.28
Bleeds	0.00	-0.93	0.00	-0.93	0.00	-1.22
AEs	0.00	-0.05	0.00	-0.05	0.00	-0.06
Total	15.03	11.86	15.03	11.86	12.78	9.55
LY, life years; QALY, quality-adjusted life year						

The results show that the QALY gain associated with the TPO-RAs is driven by increasing the time spent on treatment, with the associated benefits with respect to quality of life and mortality (via bleeds) compared to the later states in which maintenance treatment is no longer available.

Costs are driven by the acquisition and administration costs of the TPO-RAs and the costs of acquisition and administration of the rescue treatments. The incremental costs of rescue are driven by the period beyond which all maintenance options have been exhausted. The total cost of romiplostim acquisition and administration is approximately twice the cost of eltrombopag acquisition and administration in splenectomised patients. For non-splenectomised patients the total cost of romiplostim is approximately 35% higher. This reflects the higher dose of romiplostim required for splenectomised patients.

6.7.6 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table B88: Summary of QALY gain by health state (vs. non-TPO RA pathway, discounted) - splenectomised

Health state	QALY intervention (eltrombopag)	QALY comparator (non TPO RA pathway)	Increment	Absolute increment	% absolute increment	QALY intervention (romiplostim)	QALY comparator (non-TPO RA pathway)	Increment	Absolute increment	% absolute increment
On TPO-RA	3.37	0.00	3.37	3.37	56%	3.37	0.00	3.37	3.37	56%
On non TPO-RA	1.24	1.48	-0.24	0.24	4%	1.24	1.48	-0.24	0.24	4%
Off tx between maintenance tx	0.32	0.23	0.09	0.09	1%	0.32	0.23	0.09	0.09	1%
Off tx	8.37	10.52	-2.15	2.15	36%	8.37	10.52	-2.15	2.15	36%
Bleeds	-0.87	-1.03	0.17	0.17	3%	-0.87	-1.03	0.17	0.17	3%
AEs	-0.21	-0.25	0.04	0.04	1%	-0.21	-0.25	0.04	0.04	1%
Total	12.22	10.95	1.28	6.06	100%	12.22	10.95	1.28	6.06	100%
QALY, quality-adjusted life year										
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee										

Table B89: Summary of QALY gain by health state (vs. non-TPO RA pathway, discounted) - splenectomised

Health state	QALY intervention (eltrombopag)	QALY comparator (non TPO RA pathway)	Increment	Absolute increment	% absolute increment	QALY intervention (romiplostim)	QALY comparator (non-TPO RA pathway)	Increment	Absolute increment	% absolute increment
On TPO-RA	5.03	0.00	5.03	5.03	59%	5.03	0.00	5.03	5.03	59%
On non TPO-RA	1.01	1.34	-0.33	0.33	4%	1.01	1.34	-0.33	0.33	4%
Off tx between maintenance tx	0.26	0.21	0.05	0.05	1%	0.26	0.21	0.05	0.05	1%
Off tx	6.53	9.28	-2.75	2.75	32%	6.53	9.28	-2.75	2.75	32%
Bleeds	-0.93	-1.22	0.30	0.30	4%	-0.93	-1.22	0.30	0.30	4%
AEs	-0.05	-0.06	0.01	0.01	0%	-0.05	-0.06	0.01	0.01	0%
Total	11.86	9.55	2.31	8.48	100%	11.86	9.55	2.31	8.48	100%
QALY, quality-adjusted life year										
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee										

Table B90: Summary of costs by health state (vs. non-TPO RA pathway, discounted) – non splenectomised

Health state	Cost intervention (eltrombopag)	Cost comparator (non-TPO RA pathway)	Increment	Absolute increment	% absolute increment	Cost intervention (romiplostim)	Cost comparator (non-TPO RA pathway)	Increment	Absolute increment	% absolute increment
On TPO-RA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On non TPO-RA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Off tx between maintenance tx	£13,594	£12,698	£896	£896	0%	£13,594	£12,698	£896	£896	0%
Off tx	£172,587	£245,294	-£72,707	£72,707	37%	£172,587	£245,294	-£72,707	£72,707	30%
Bleeds	£27,483	£36,060	-£8,577	£8,577	4%	£27,483	£36,060	-£8,577	£8,577	4%
AEs	£0	£0	£0	£0	0%	£0	£0	£0	£0	0%
Total	£332,193	£297,292	£34,900	£199,183	100%	£372,744	£297,292	£75,452	£239,735	100%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee										

Table B91: Summary of costs by health state (vs. non-TPO RA pathway, discounted) – non splenectomised

Health state	Cost intervention (eltrombopag)	Cost comparator (non-TPO RA pathway)	Increment	Absolute increment	% absolute increment	Cost intervention (romiplostim)	Cost comparator (non-TPO RA pathway)	Increment	Absolute increment	% absolute increment
On TPO-RA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On non TPO-RA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Off tx between maintenance tx	£30,020	£25,023	£4,997	£4,997	3%	£30,020	£25,023	£4,997	£4,997	2%
Off tx	£415,911	£522,996	-£107,084	£107,084	54%	£415,911	£522,996	-£107,084	£107,084	37%
Bleeds	£24,954	£29,497	-£4,543	£4,543	2%	£24,954	£29,497	-£4,543	£4,543	2%
AEs	£0	£0	£0	£0	0%	£0	£0	£0	£0	0%
Total	£556,089	£581,073	-£24,984	£199,523	100%	£643,598	£581,073	£62,525	£287,032	100%

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table B92: Summary of predicted resource use by category of cost, splenectomised patients

Item	Cost intervention (eltrombopag)	Cost comparator (non TPO-RA pathway)	Increment	Absolute increment	% absolute increment	Cost intervention (romiplostim)	Cost comparator (non TPO-RA pathway)	Increment	Absolute increment	% absolute increment
TPO-RA Acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPO-RA Administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non TPO-RA Acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non TPO-RA Administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rescue Acquisition	£301,752	£370,832	-£69,080	£69,080	36%	£301,752	£370,832	-£69,080	£69,080	25%
Rescue Administration	£144,180	£177,187	-£33,007	£33,007	17%	£144,180	£177,187	-£33,007	£33,007	12%
Bleeds	£24,954	£29,497	-£4,543	£4,543	2%	£24,954	£29,497	-£4,543	£4,543	2%
Total	£556,089	£581,073	-£24,984	£189,529	100%	£643,598	£581,073	£62,525	£277,037	100%

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table B93: Summary of predicted resource use by category of cost, non-splenectomised patients

Item	Cost intervention (eltrombopag)	Cost comparator (non TPO-RA pathway)	Increment	Absolute increment	% absolute increment	Cost intervention (romiplostim)	Cost comparator (non TPO-RA pathway)	Increment	Absolute increment	% absolute increment
TPO-RA Acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPO-RA Administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non TPO-RA Acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non TPO-RA Administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rescue Acquisition	£119,178	£165,145	-£45,968	£45,968	23%	£119,178	£165,145	-£45,968	£45,968	19%
Rescue Administration	£67,003	£92,846	-£25,843	£25,843	13%	£67,003	£92,846	-£25,843	£25,843	11%
Bleeds	£27,483	£36,060	-£8,577	£8,577	4%	£27,483	£36,060	-£8,577	£8,577	4%
Total	£332,193	£297,292	£34,900	£197,392	100%	£372,744	£297,292	£75,452	£237,943	100%

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Base-case analysis

6.7.7 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Table B94 and Table B95 present the base case results for splenectomised and non-spelenectomised patients.

Table B94. Base case results - splenectomised

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	ICER (£/QALY) versus non TPO-RA pathway
Eltrombopag	£556,089	15.56	12.22	£0	0.00	0.00	Referent	Dominates
Non TPO-RA pathway	£581,073	14.35	10.95	£24,984	-1.20	-1.28	Dominated	Referent
Romiplostim	£643,598	15.56	12.22	£87,508	0.00	0.00	Dominated	£48,914
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years Slight discrepancies are due to rounding.								

Table B95. Base case results – non splenectomised

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	ICER (£) versus non TPO-RA pathway
Non TPO-RA pathway	£297,292	12.78	9.55	£0	0.00	0.00	Referent	Referent
Eltrombopag	£332,193	15.03	11.86	£34,900	2.25	2.31	£15,105	£15,105
Romiplostim	£372,744	15.03	11.86	£40,552	0.00	0.00	Dominated	£32,657
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years Slight discrepancies are due to rounding.								

Sensitivity analyses

6.7.8 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Deterministic sensitivity analyses were undertaken as one-way sensitivity analyses by varying individual parameters relative to their base case values. Section 6.6.2 discusses the parameters that were varied and the approach to DSA. The full results are presented in Table B96 and Table B97.

Table B96: Deterministic sensitivity analyses - splenectomised

Deterministic sensitivity analyses	Incr. Costs			Incr. QALYs			ICER £/QALY		
	Eltrombopag	Romiplostim	Non TPO-RA pathway	Eltrombopag	Romiplostim	Non TPO-RA pathway	Eltrombopag	Romiplostim	Non TPO-RA pathway
Treatment pathway									
TPO-RA received prior to rituximab	£0	£87,508	£23,223	0.00	0.00	-1.21	Referent	Dominated	Dominated
TPO as last active treatment (compared to no active treatment)	£0	£87,508	£30,867	0.00	0.00	-1.38	Referent	Dominated	Dominated
Rituximab replaced by TPO in sequence	£0	£87,508	£12,228	0.00	0.00	-0.93	Referent	Dominated	Dominated
Efficacy parameters									
Odds ratio of 1.0 for TPO comparison, baseline overall response as per Kuter 2008 definition estimated from RAISE	£0	£69,183	£17,658	0.00	0.00	-0.96	Referent	Dominated	Dominated
Odds ratio taken from indirect comparison, applied to baseline overall response as per Kuter 2008 definition estimated from RAISE	£0	£95,649	£19,075	0.00	0.56	-1.02	Referent	£171,156	Dominated
Time on treatment, responders, log-logistic	£0	£83,622	£23,543	0.00	0.00	-1.23	Referent	Dominated	Dominated
Time on treatment, responders, Gamma	£0	£93,305	£27,411	0.00	0.00	-1.35	Referent	Dominated	Dominated
Time on treatment, all patientsGompertz	£0	£102,692	£33,099	0.00	0.00	-1.41	Referent	Dominated	Dominated
Time on treatment, all patients,log-logistic	£0	£80,300	£22,823	0.00	0.00	-1.17	Referent	Dominated	Dominated
Time on treatment, all patients, Weibull	£0	£57,558	£13,626	0.00	0.00	-0.90	Referent	Dominated	Dominated
Mortality modelled via platelet level rather than bleeds	£0	£87,537	£38,927	0.00	0.00	-1.04	Referent	Dominated	Dominated

Deterministic sensitivity analyses	Incr. Costs			Incr. QALYs			ICER £/QALY		
	Eltrombopag	Romiplostim	Non TPO-RA pathway	Eltrombopag	Romiplostim	Non TPO-RA pathway	Eltrombopag	Romiplostim	Non TPO-RA pathway
Rescue rates for patients with platelets <50 x10^9 (per month)									
RAISE rate -25%	£45,829	£133,289	£0	1.64	1.64	0.00	£27,957	Dominated	Referent
RAISE rate	£34,746	£122,214	£0	1.58	1.58	0.00	£21,967	Dominated	Referent
Mid point RAISE 2008 and TA221	£7,076	£94,564	£0	1.44	1.44	0.00	£4,914	Dominated	Referent
TA221	£0	£87,508	£24,984	0.00	0.00	-1.28	Referent	Dominated	Dominated
TA221 +25%	£0	£87,527	£60,094	0.00	0.00	-1.10	Referent	Dominated	Dominated
Proportion of rescue treatment									
IVIg + 25%	£0	£87,504	£54,886	0.00	0.00	-1.28	Referent	Dominated	Dominated
IVIg – 25%	£0	£87,476	£24,511	0.00	0.00	-1.51	Referent	Dominated	Dominated
Rate of serious bleeds for patients with <50 x 10^9 (per month)									
RAISE rate -25%	£0	£87,595	£72,065	0.00	0.00	-0.36	Referent	Dominated	Dominated
RAISE rate	£0	£87,594	£71,243	0.00	0.00	-0.37	Referent	Dominated	Dominated
Mid point RAISE 2008 and TA221	£0	£87,551	£44,790	0.00	0.00	-0.89	Referent	Dominated	Dominated
TA221	£0	£87,508	£24,984	0.00	0.00	-1.28	Referent	Dominated	Dominated
TA221 +25%	£0	£87,486	£16,540	0.00	0.00	-1.44	Referent	Dominated	Dominated

Deterministic sensitivity analyses	Incr. Costs			Incr. QALYs			ICER £/QALY		
	Eltrombopag	Romiplostim	Non TPO-RA pathway	Eltrombopag	Romiplostim	Non TPO-RA pathway	Eltrombopag	Romiplostim	Non TPO-RA pathway
Costs									
All patients receive romiplostim as outpatient visit	£0	£117,132	£24,984	0.00	0.00	-1.28	Referent	Dominated	Dominated
No PAS for eltrombopag	£0	[redacted]	[redacted]	0.00	0.00	-1.28	Referent	Dominated	Dominated
Romiplostim dose from Bussel 2009	£0	£146,054	£24,984	0.00	0.00	-1.28	Referent	Dominated	Dominated
Decision maker parameters									
Discount rate = 0%	£0	£118,077	£9,560	0.00	0.00	-2.30	Referent	Dominated	Dominated
Discount rate= 6%	£0	£74,447	£27,326	0.00	0.00	-0.92	Referent	Dominated	Dominated
Time horizon 6 months	£0	£6,949	£1,877	0.00	0.00	-0.02	Referent	Dominated	Dominated
Time horizon 5 years	£0	£43,997	£20,965	0.00	0.00	-0.21	Referent	Dominated	Dominated
Time horizon 10 years	£0	£62,487	£35,432	0.00	0.00	-0.45	Referent	Dominated	Dominated
Time horizon 20 years	£0	£78,568	£36,987	0.00	0.00	-0.85	Referent	Dominated	Dominated
Structural sensitivity analyses									
Bleed risk in final non-responder state same as other non-responder states	£0	£58,339	£21,250	0.00	0.00	-1.19	Referent	Dominated	Dominated

Table B97: Deterministic sensitivity analyses - non splenectomised

Deterministic sensitivity analyses	Incr. Costs			Incr. QALYs			ICER £/QALY		
	Eltrombopag	Romiplostim	Non TPO-RA pathway	Eltrombopag	Romiplostim	Non TPO-RA pathway	Eltrombopag	Romiplostim	Non TPO-RA pathway
Treatment pathway									
TPO-RA received prior to rituximab	£35,001	£75,552	£0	2.19	2.19	0.00	£15,996	Dominated	Referent
TPO-RA as last active treatment (compared to no active treatment)	£32,051	£72,603	£0	2.48	2.48	0.00	£12,898	Dominated	Referent
Rituximab replaced by TPO-RA in sequence	£36,668	£77,220	£0	1.88	1.88	0.00	£19,463	Dominated	Referent
Efficacy parameters									
Odds ratio of 1.0 for TPO comparison, baseline overall response as per Kuter 2008 definition estimated from RAISE	£31,710	£68,252	£0	1.97	1.97	0.00	£16,073	Dominated	Referent
Odds ratio taken from indirect comparison, applied to baseline overall response as per Kuter 2008 definition estimated from RAISE	£31,619	£83,035	£0	2.08	2.55	0.00	£15,177	£110,983	Referent
Time on treatment, responders, log-logistic	£33,552	£71,923	£0	2.20	2.20	0.00	£15,235	Dominated	Referent
Time on treatment, responders, Gamma	£35,852	£78,168	£0	2.39	2.39	0.00	£14,987	Dominated	Referent
Time on treatment, all patients, Gompertz	£37,588	£86,256	£0	2.62	2.62	0.00	£14,347	Dominated	Referent
Time on treatment, all patients, log-logistic	£30,455	£65,141	£0	1.99	1.99	0.00	£15,305	Dominated	Referent
Time on treatment, all patients,Weibull	£26,684	£54,511	£0	1.67	1.67	0.00	£15,995	Dominated	Referent
Mortality modelled via platelet level rather than bleeds	£18,642	£59,216	£0	1.84	1.84	0.00	£10,112	Dominated	Referent

Deterministic sensitivity analyses	Incr. Costs			Incr. QALYs			ICER £/QALY		
	Eltrombopag	Romiplostim	Non TPO-RA pathway	Eltrombopag	Romiplostim	Non TPO-RA pathway	Eltrombopag	Romiplostim	Non TPO-RA pathway
Rescue rates for patients with platelets <50 x10^9 (per month)									
RAISE rate -25%	£84,364	£124,904	£0	2.55	2.55	0.00	£33,106	Dominated	Referent
RAISE rate	£76,936	£117,478	£0	2.51	2.51	0.00	£30,623	Dominated	Referent
Mid point RAISE 2008 and TA221	£34,900	£75,452	£0	2.31	2.31	0.00	£15,105	Dominated	Referent
TA221	£34,900	£75,452	£0	2.31	2.31	0.00	£15,105	Dominated	Referent
TA221 +25%	£14,367	£54,922	£0	2.21	2.21	0.00	£6,492	Dominated	Referent
Proportion of rescue treatment									
IVIg +25%	£26,035	£66,588	£0	2.28	2.28	0.00	£11,439	Dominated	Referent
IVIg -25%	£43,911	£84,461	£0	2.34	2.34	0.00	£18,726	Dominated	Referent
Rate of serious bleeds for patients with <50 x 10^9 (per month)									
RAISE rate -25%	£0	£40,609	£10,705	0.00	0.00	-0.62	Referent	Dominated	Dominated
RAISE rate	£0	£40,608	£9,833	0.00	0.00	-0.65	Referent	Dominated	Dominated
Mid point RAISE 2008 and TA221	£16,806	£57,385	£0	1.65	1.65	0.00	£10,203	Dominated	Referent
TA221	£34,900	£75,452	£0	2.31	2.31	0.00	£15,105	Dominated	Referent
TA221 +25%	£42,125	£82,661	£0	2.57	2.57	0.00	£16,381	Dominated	Referent

Deterministic sensitivity analyses	Incr. Costs			Incr. QALYs			ICER £/QALY		
	Eltrombopag	Romiplostim	Non TPO-RA pathway	Eltrombopag	Romiplostim	Non TPO-RA pathway	Eltrombopag	Romiplostim	Non TPO-RA pathway
Costs									
All patients receive romiplostim as outpatient visit	£34,900	£119,960	£0	2.31	2.31	0.00	£15,105	Dominated	Referent
No PAS for eltrombopag	[redacted]	£117,914	£0	2.31	2.31	0.00	[redacted]	Dominated	Referent
Romiplostim dose from Bussel 2009	£34,900	£160,173	£0	2.31	2.31	0.00	£15,105	Dominated	Referent
Decision maker parameters									
Discount rate = 0%	£74,241	£132,010	£0	4.22	4.22	0.00	£17,583	Dominated	Referent
Discount rate= 6%	£22,444	£55,948	£0	1.64	1.64	0.00	£13,700	Dominated	Referent
Time horizon 6 months	£1,840	£4,259	£0	0.02	0.02	0.00	£74,250	Dominated	Referent
Time horizon 5 years	£4,324	£21,641	£0	0.33	0.33	0.00	£13,022	Dominated	Referent
Time horizon 10 years	£4,643	£30,866	£0	0.76	0.76	0.00	£6,132	Dominated	Referent
Time horizon 20 years	£15,694	£50,675	£0	1.50	1.50	0.00	£10,467	Dominated	Referent
Structural sensitivity analyses									
Bleed risk in final non-responder state same as other non-responder states	£0	£33,184	£3,006	0.00	0.00	-1.62	Referent	Dominated	Dominated

6.7.9 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

The results of the probabilistic sensitivity analysis for the base case are presented as distributions of simulations on the cost-effectiveness plane (Figure B24 and Figure B26) and as cost-effectiveness acceptability frontiers (Figure B25 and Figure B27).

Figure B24: Distributions of simulations on the cost-effectiveness plane –splenectomised patients

Figure B25: Cost-effectiveness acceptability frontier – splenectomised patients

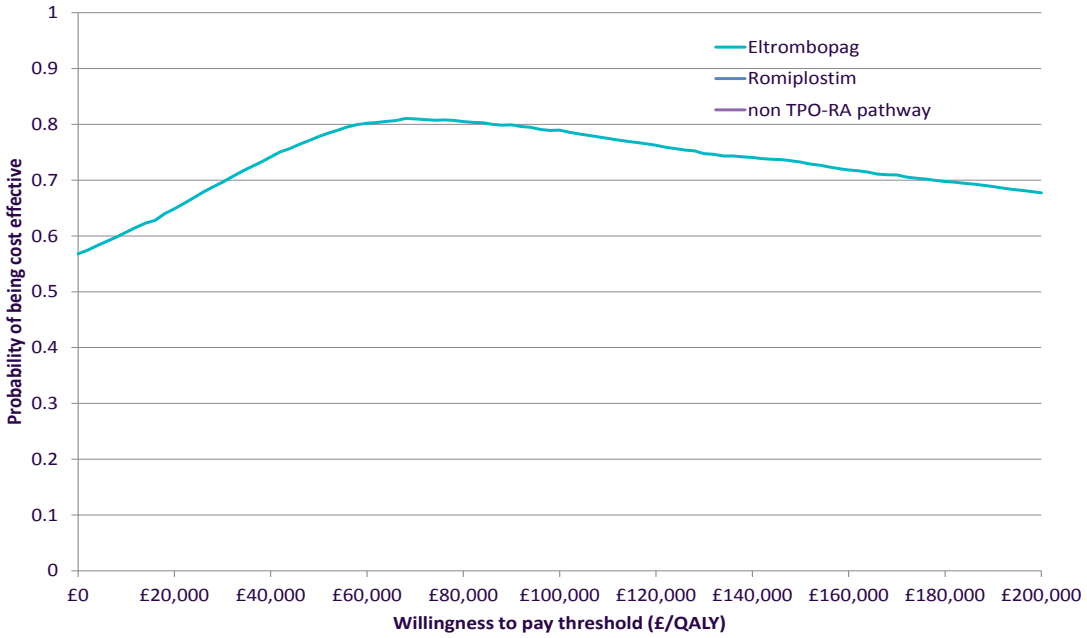
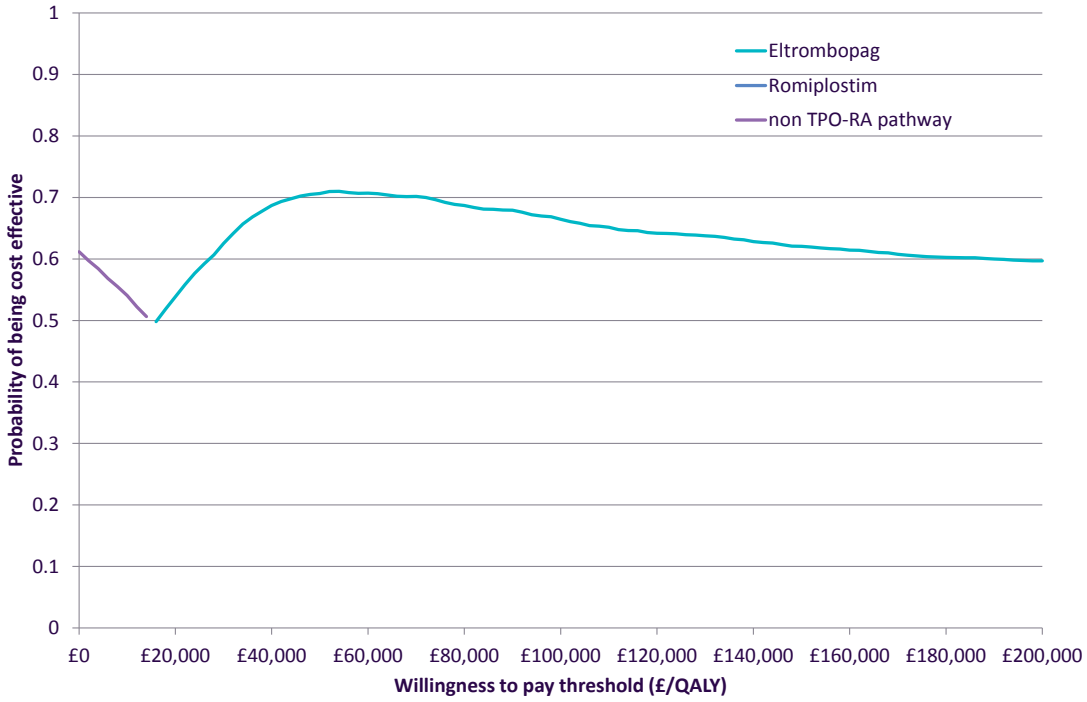


Figure B26: Distributions of simulations on the cost-effectiveness plane –non- splenectomised patients

Figure B27: Cost-effectiveness acceptability frontier – non-splenectomised patients



6.7.10 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

The alternative evaluation explores the cost effectiveness of eltrombopag, using data from the eltrombopag clinical trial program to relate short term trial data to lifetime costs and outcomes. This analysis also incorporates the most recent evidence from an updated systematic review.

Table B98 and Table B99 show the cost-effectiveness results for this scenario. Probabilistic sensitivity analyses for this scenario are provided in Appendix 16.

Table B98: Cost-effectiveness results for the alternative evaulation, splenectomised patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY) Incremental	ICER (£/QALY) versus non TPO-RA pathway
Non TPO-RA pathway	£281,654	17.82	13.94	£0	0.00	0.00	Referent	Referent
Eltrombopag	£315,148	18.17	14.48	£33,495	0.35	0.55	£61,337	£61,337
Romiplostim	£402,259	18.17	14.48	£120,605	0.35	0.55	Dominated	£220,860
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table B99: Cost-effectiveness results for the alternative evaluation, non-splenectomised patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY) incremental	ICER (£/QALY) versus non TPO-RA pathway
Non TPO-RA pathway	£158,390	17.70	14.19	£0	0.00	0.00	Referent	Referent
Eltrombopag	£232,335	18.25	14.96	£73,945	0.55	0.77	£95,536	£95,536
Romiplostim	£272,680	18.25	14.96	£114,290	0.55	0.77	Dominated	£147,660
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Results for a scenario using all available assumptions from TA221 (as outlined in section 6.6.2are provided in Table B100 and Table B101.

Table B100: Results for scenario analysis incorporating all assumptions in TA221, splenectomised

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY) Incremental	ICER (£/QALY) versus non TPO-RA pathway
Eltrombopag	£575,374	15.85	12.28	£0	0.00	0.00	Referent	Dominates
Non TPO-RA pathway	£596,624	14.65	11.09	£21,250	-1.20	-1.19	Dominated	Referent
Romiplostim	£633,714	15.85	12.28	£58,339	0.00	0.00	Dominated	£31,062
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years Any discrepencies are due to rounding								

Table B101: Results for scenario analysis incorporating all assumptions in TA221, non splenectomised

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY) incremental	ICER (£/QALY) versus non TPO-RA pathway
Eltrombopag	£472,641	15.50	12.08	£0	0.00	0.00	Referent	Dominates
Non TPO-RA pathway	£475,646	13.81	10.45	£3,006	-1.69	-1.62	Dominated	Referent
Romiplostim	£505,824	15.50	12.08	£33,184	0.00	0.00	Dominated	£18,578
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years Any discrepencies are due to rounding								

6.7.11 What were the main findings of each of the sensitivity analyses?

Deterministic analyses - multi-way

Alternative evaluation

In the alternative evaluation neither eltrombopag nor romiplostim are cost-effective versus a non TPO-RA pathway in splenectomised or non splenectomised patients. In this scenario the incremental costs of TPO-RAs are increased, due to the lower rescue rates, and the incremental QALYs are reduced due to a lower impact of platelet level on inpatient bleeds and thus mortality.

Analysis incorporating all available assumptions from TA221

A sensitivity analysis was run to try to reflect, as far as possible the data used in the

TA221 analysis, details of this analysis are presented in Section 6.6.2. In this scenario romiplostim remains dominated by eltrombopag. However, when compared to the non TPO-RA pathway the ICERs are £31,062/QALY for splenectomised patients and £18,578/QALY for non-splenectomised patients. This scenario is associated with some uncertainty, particularly as the number of 250µg vials of romiplostim required for each subgroup was marked as commercial in confidence in the submission and therefore had to be approximated. However, the results do indicate that under plausible assumptions romiplostim may be a cost-effective treatment when compared to a non TPO-RA pathway in this model.

Deterministic sensitivity analyses – one-way

For splenectomised patients the results are relatively insensitive to the scenarios that were explored. Eltrombopag dominates the non TPO-RA pathway in all scenarios offering a cost saving of between £1,877 (6 month time horizon) and £46,380 (bleed risk in final non-responder state same as in other non-responder states) and a QALY gain of 0.02 (6 month time horizon) to 2.30 (discount rate set to 0% for costs and benefits). Eltrombopag dominates romiplostim in all scenarios with the exception of when the odds ratio from the indirect comparison is used to estimate the relative efficacy of the TPO-RAs with respect to response. In this scenario romiplostim offers 0.56 additional QALYs compared to eltromboag, however at an additional cost of £95,649 for romiplostim the ICER for romiplostim vs. eltrombopag is £171,156/QALY. Given that the results of the indirect comparison were not significant, that the inherent uncertainty in such a comparison was compounded by small patient numbers (orphan disease) and the heterogenous nature of cITP, and that the clinical community view the TPO-RAs as interchangeable, the QALY difference in this analysis is not considered clinically meaningful.

For non-splenectomised patients the ICER remains below £20,000 per QALY in all scenarios with the exception of when a 6 month time horizon is used (ICER = £74,250/QALY). Again, eltrombopag dominates romiplostim in all scenarios with the exception of when the odds ratio from the indirect comparison is used to estimate the relative efficacy of the TPO-RAs with respect to response. In this scenario romiplostim offers 0.46 additional QALYs compared to eltromboag, however at an additional £51,416 for romiplostim the ICER for romiplostim vs. eltrombopag is £110,983/QALY

Rescue rates, the relative proportions of different rescue types used and bleeding rates have a significant impact on cost-effectiveness, however when considered in a univariate manner the ICERs for eltrombopag remain below £33,000/QALY in all scenarios.

Probabilistic sensitivity analysis

Probabilities that eltrombopag is cost-effective at £20,000; £25,000 and £30,000 per QALY thresholds are shown in Table B102.

Table B102: Probability eltrombopag is cost-effective in base case analysis.

Threshold	Splenectomised patients	Non-splenectomised patients
£20,000/QALY	65%	54%
£25,000/QALY	67%	59%
£30,000/QALY	70%	63%

6.7.12 What are the key drivers of the cost-effectiveness results?

Cost-effectiveness versus a non TPO-RA pathway

The results of the deterministic sensitivity analyses and of alternative evaluation (where a higher rescue rate is assumed) demonstrate that the assumed rates of rescue for patients with platelet counts less than 50 x 10^9/L is a key driver of cost-effectiveness of eltrombopag versus a non TPO-RA pathway. The higher the rate of rescue, the more cost-effective TPO-RAs become.

There is uncertainty as to the true rate of rescue for people with chronic ITP in clinical practice, particularly the use of expensive IVIg. The rates of rescue used in the base case analysis are based on assumptions made in TA221 and are higher than those assumed in alternative evaluation (estimated from RAISE/EXTEND data). The rates assumed in TA221 are assumed to be reflective of the rates in the romiplostim pivotal trials although full details of how they were calculated are not available. Rates of rescue in RAISE/EXTEND may have been lower due to greater heterogeneity in treatment practice across the countries in which the trial took place and a higher use of concomitant medications in RAISE (refer to section 5.7).

A retrospective study of resource use in 610 patients (70 from the UK) with chronic ITP, analysed for this appraisal, demonstrated that 15% of patients received at least one IVIg infusion over the 12 month observational period. The use of IVIg alone contributed to at least 43% of average management costs and as much as 70% of costs in patients that received at least one IVIg infusion (see appendix 18). The baseline median platelet count in this study was 70 x10^9/L and ~40% of patients did not receive any treatment over the 12 month observational period. This suggests that the study was carried out in a less severe population than the eltrombopag and romiplostim clinical trials. The patients that had received at least one IVIg infusion and had been hospitalized at least once are more reflective of the patients in the TPO-RA trials as they had a median baseline platelet count of 21 x10^9/L and ~50% of them had received more than 3 treatments over the observational period. The higher rates of rescue used in the base case are therefore likely to be realistic estimates of rescue for at least some patients. 5 case studies of chronic ITP patients in UK clinical practice further demonstrate the frequent use of rescue medication in some patients (Appendix 13).

As evidenced by the deterministic sensitivity analyses, cost-effectiveness of eltrombopag versus a non-TPO-RA pathway is also sensitive to the rate of bleeding events, albeit to a lesser extent. Where lower bleeding rates were incorporated into the model, the cost-effectiveness estimates for TPO-RAs increased. Bleed rates are generally lower in the RAISE/EXTEND analysis compared to those used in the TA221 analysis. However, it should be noted that we have had to derive romiplostim's bleed rates based on the reported probabilistic parameters in the manufacturer's submission for TA221 as information regarding bleed rates was marked as commercial in confidence in the available submission

document. Any comparison of these rates should therefore be treated with caution. Again which assumptions about bleeding rates are most applicable to clinical practice is uncertain.

Other drivers of cost-effectiveness that have a smaller impact on results are:

- Positioning of eltrombopag in the treatment pathway: Positioning TPO-RAs prior to ritximab increases ICERs versus a non TPO-RA pathway whereas positioning TPO-RAs at the end of the treatment pathway results in TPO-RAs becoming more cost-effective.
- Method for incorporating mortality into the model: Modelling mortality conditional on platelet level improves the cost-effectiveness of TPO-RAs.
- Inclusion of a PAS for eltrombopag: Removal of the PAS reduces the cost-effectivenss of eltrombopag.
- Dosing assumptions used for romiplostim: Utilising data from the romiplostim extension study results in higher ICERs for romiplostim versus a non TPO-RA pathway.

Cost-effectiveness versus romiplostim

The key driver of cost effectiveness versus romiplostim is the relative cost of the TPO-RAs. The sensitivity analysis that incorporates the point estimate from the indirect comparison of overall response does not change the overall interpretation of results. Although eltrombopag accrues slightly fewer QALYs than romiplostim, it is significantly cheaper and can be considered cost-effective.

6.8 Validation

6.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

Two levels of validation took place. The first assessed whether the methods underpinning the model and results were appropriate. The second addressed the technical validity of the model. Documentation is available on request.

6.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

6.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

Other than for splenectomised and non-splenectomised patients no further subgroup analyses were undertaken.

6.9.2 Please clearly define the characteristics of patients in the subgroup.

N/A

6.9.3 Please describe how the statistical analysis was undertaken.

N/A

6.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.7.6 (Base-case analysis).

N/A

6.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 4.

N/A

6.10 Interpretation of economic evidence

6.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The previous technology appraisals of eltrombopag (TA205) and romiplostim (TA221) and their associated economic evaluations have been published. We do not discuss the previous eltrombopag submission here, however we have discussed how the results of romiplostim versus a non-TPO RA compare in our base case with those reported in TA221.

Eltrombopag is cost effective versus a non-TPO-RA pathway in the base case model, which uses assumptions most relevant to the decision problem, including some of the assumptions made in TA221 where this is considered appropriate.

Romiplostim is not cost effective versus a non TPO-RA pathway in the base case model and as such does not reflect the ICERs considered most plausible in TA221. This is likely due to the differing assumptions regarding response rates, romiplostim dosing, the positioning of TPO-RAs in the treatment pathway and the calibration of rescue rates in TA221. A sensitivity analysis aimed to more fully incorporate the assumptions which underpin the recommendation for romiplostim. It was not possible to incorporate these fully as a significant amount of information was marked as commercial in confidence in the TA221 documents, but this sensitivity analysis confirms that romiplostim is a cost-effective treatment option under a set of plausible assumptions.

The alternative evaluation in this submission – in which the model incorporates alternative available evidence considered relevant to the decision problem, suggests that neither eltrombopag nor romiplostim are cost-effective versus a non TPO-RA pathway. This is largely driven by the lower rescue and bleeding rates for patients with a platelet count of ≤50 x 10^9/L used in this analysis. In a severe refractory cITP population (for which romiplostim is recommended by NICE) the higher rates are more likely to be applicable, as supported by observational data and clinical case studies in this patient group.

Importantly, all scenarios demonstrate that eltrombopag is a cost-effective treatment option compared to romiplostim – the current standard of care. Eltrombopag should therefore be recommended as a convenient, oral alternative to romiplostim for the treatment of cITP on the basis that there is no evidence of a difference in efficacy between the TPO-RAs, that they are considered interchangeable by the clinical community and that eltrombopag is significantly cost-saving.

6.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

This evaluation is relevant to all patients who, according to the European licence for eltrombopag) could potentially use eltrombopag (and romiplostim).

6.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Strengths

- Costs and benefits were estimated over a lifetime time horizon.
- A comprehensive approach to sensitivity analysis has been taken, exploring a wide range of possible uncertainties.
- Scenario analyses were conducted to explore the impact of alternative sources of evidence and to understand the sensitivities of the modelling approach.
- This evaluation incorporates a comparison with both romiplostim – the current standard of care – and a non TPO-RA pathway.
- The economic model is flexible, enabling the user to explore different treatment pathways and alternative positioning of TPO-RAs within a pathway.

Limitations

- Clinical evidence – no head to head randomised trial evidence was available to compare any of the comparators considered. Due to the presence of a common comparator an adjusted indirect comparison was possible for the comparison of the TPO-RAs. This comparison was associated with considerable uncertainty and potentially bias, as outlined in section 5.7. Comparisons of the TPO-RAs to non TPO-RA therapies could not be based on robust indirect comparisons due to a lack of randomised evidence for the non TPO-RA treatments. Estimates of the efficacy of these treatments were therefore based on a naïve indirect comparison approach, which has well known limitations due to the potential differences in study design, quality and patient populations across included studies.
- Treatment pathway – the treatment pathway for refractory cITP patients is not well defined, and choice regarding therapy type and number of therapy lines are made at the discretion of the treating physician. However, our analysis suggests that the results of the model are relatively insensitive to alternative treatment pathways.
- Mortality – the probability of death from cITP is estimated from US data regarding the probability of death conditional upon hospitalisation. Patients in the US may be hospitalised for less severe bleeding symptoms. If this is the case the rate of death may be underestimated in the model. In addition, emergency room visits resulting in hospitalisations were not included in this study. These would likely have been associated with higher rates of death, again this may reduce the rate of death associated with inpatient hospitalisations and thus the benefit of the TPO-RAs.
- Platelet measurement – platelet level at the onset of bleeds and rescue treatments was not always measured, this required us to use a linear interpolation approach to estimate the platelet level at the time of important events. This may have led to bleed and rescue events being allocated to higher platelet levels than would have been observed with better measurement.
- Treatment modality - no attempt was made to incorporate the benefit of an oral therapy. This may be associated with a utility gain compared to an injection based

treatment or the intravenous treatments used at points in the non TPO-RA pathway.

- Long-term prognosis – the long term outcomes for patients who have run out of maintenance treatments are unknown. An attempt was made to adjust for this by increasing the rate of inpatient bleeds at this point. However, other events (day case bleeds, rescue events) may also increase at this point, thus increasing the value of reducing time spent in this state.
- Oral steroid use – oral steroid use at baseline in both the RAISE and Kuter 2008 trials was high. Although oral steroids are inexpensive, their long term use is associated with adverse effects. Thus reducing the intensity or period of oral steroid use may be another substantive benefit of TPO-RA treatment which is not captured in the current model.

6.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

A source of uncertainty in the economic case for eltrombopag lies in the comparative evidence of eltrombopag versus romiplostim. In the absence of head to head data this has been established through an indirect comparison. In an orphan disease area where treatment practice is variable, the results are not unexpectedly uncertain. To inform this consideration, we estimated the sample size that would be required to demonstrate both equivalence and non-inferiority in a RCT of eltrombopag versus romiplostim.

The sample size required for an equivalence RCT with platelet response as the primary endpoint and a tolerance limit of 5% is 2,873, while 2,273 patients would be required to demonstrate non-inferiority. If clinically significant bleeding was selected as the primary endpoint this would increase to 3,828 (3,030 for non-inferiority).

Given the low incidence of cITP (approximately 2.4% of all patients with ITP) it would not be feasible to conduct such a trial.

There is also uncertainity surrounding the risk of receiving rescue medications which is unlikely to be alleviated by further studies. As a result of the orphan and heterogenous nature of the disease, the use of rescue treatment is likely to vary significantly depending on the individual patient and the experience of the clinician. However the small population of severe, refractory cITP patients addressed in this decision problem are likely to require frequent rescue treatments.

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

7.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

Table B103 shows the number of patients in England and Wales assumed to be eligible to receive a TPO-RA in 2012-2017. These calculations are based on ONS 2010-based population projections, the prevalence of ITP in the UK[1] and the assumptions used in the NICE costing template for romiplostim.[31] The split of splenectomised and non splenectomised patients has been assumed to be similar to that in the RAISE trial (37% splenectomised).

Table B103. Eligible patient population

Eligible patient population	Reference							
			2012	2013	2014	2015	2016	2017
Population >18 (England and Wales)	ONS 2010 based population projections		43,646,714	44,026,040	44,385,063	44,736,527	45,086,615	45,413,261
Patients with ITP (UK prevalence)	Bennett 2011	0.05%	21,823	22,013	22,193	22,368	22,543	22,707
Patients requiring treatment	NICE costing template for romiplostim	60%	13,094	13,208	13,316	13,421	13,526	13,624
1st line treatment unsuccessful	NICE costing template for romiplostim	67%	8,773	8,849	8,921	8,992	9,062	9,128
Patients refractory to 1st line treatment that require long term treatment	NICE costing template for romiplostim	40%	3,509	3,540	3,569	3,597	3,625	3,651
Patients remitting or responding to other treatments	NICE costing template for romiplostim	85%	2,983	3,009	3,033	3,057	3,081	3,104
Patients eligible to use a TPO-RA	NICE costing template for romiplostim	15%	526	531	535	540	544	548
Eligible splenectomised patients	Assumption	37%	195	196	198	200	201	203
Eligible non splenectomised patients	Assumption	63%	332	335	337	340	343	345

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

It has been assumed that eligible patients are currently receiving eltrombopag, romiplostim or a non TPO-RA treatment strategy. IMS sales data (May 2012) has been used to estimate market share (i.e. the number of patients currently receiving romiplostim and eltrombopag on the basis of quantity of drug sold). The remaining eligible patients, as defined in section 7.1, have been assumed to be receiving non TPO-RA treatments. Positive guidance for eltrombopag has been assumed to result in equal market share for the two TPO-RAs. This reflects a market research survey demonstrating patients and clinicians have a similar preference for the two drugs.[37]

7.3 What assumption(s) were made about market share (when relevant)?

Table B104 shows the market share assumptions used to estimate the budgetary impact of positive NICE guidance for eltrombopag, as outlined above.

Table B104: Market share assumptions

	Reference	Patients	Current market share	Market share assuming positive guidance for eltrombopag
Total eligible patients	Section 7.1	526	100%	100%
Romiplostim patients	[redacted]	[redacted]	[redacted]	[redacted]
Eltrombopag patients	[redacted]	[redacted]	[redacted]	[redacted]
Non TPO-RA patients		[redacted]	[redacted]	[redacted]

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

Administration costs and the cost of follow up have been incorporated into the budget impact estimates. After the first 4 weeks of romiplostim treatment it has been assumed that ~70% of patients will self administer at home. If this is not the case in clinical practice, costs for romiplostim may have been underestimated.

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Costs for the first year of treatment have been taken from the economic model. Unit costs are outlined in section 6.5.

7.6 Were there any estimates of resource savings? If so, what were they?

Savings are estimated to be made as a result of the lower acquisition and administration cost of eltrombopag compared to romiplostim. Positive guidance for eltrombopag is estimated to save £13,245 annually per splenectomised patient and £4,675 annually per non-splenectomised patient if eltrombopag is used in place of romiplostim.

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

Budget impact estimates for splenectomised and non splenectomised patients are shown in Table B105 and Table B106. The eligible patient population has been estimated from ONS 2010 based population projections. Market share assumptions are defined above.

Table B105: **Annual budget impact estimates for splenectomised patients**

Budget impact 2013 – Splenectomised				
	Treatment strategy			
Annual costs	**Eltrombopag**	**Romiplostim**	**Non TPO-RA**	**Total**
Annual costs per person				
TPO-RA acquisition cost	£12,947	£23,705	£0	
TPO-RA admin cost	£1,312	£3,799	£0	
Non TPO-RA acquisition cost	£14	£14	£45	
Non TPO-RA admin cost	£310	£310	£1,227	
Rescue acquisition cost	£8,190	£8,190	£18,305	
Rescue administration cost	£3,913	£3,913	£8,746	
Total annual cost/patient	£26,687	£39,932	£28,324	
Current market share	8%	49%	44%	
Patient share	16	96	86	
Budget impact	£419,425	£3,843,936	£2,448,268	£6,711,629
Market share assuming positive guidance for eltrombopag	28%	28%	44%	
Patient share	55	55	86	
Budget impact	£1,467,987	£2,196,535	£2,448,268	£6,112,790
Cost difference	-£1,048,562	£1,647,401	£0	**£598,839**

Table B106: Annual budget impact estimates for non splenectomised patients

Budget Impact 2013 - Non splenectomised				
	Treatment strategy			
Annual costs	**Eltrombopag**	**Romiplostim**	**Non TPO-RA**	**Total**
Annual costs per person				
TPO-RA acquisition cost	£13,870	£15,819	£0	
TPO-RA admin cost	£1,464	£4,189	£0	
Non TPO-RA acquisition cost	£11	£11	£48	
Non TPO-RA admin cost	£236	£236	£1,198	
Rescue acquisition cost	£3,239	£3,239	£9,476	
Rescue administration cost	£1,821	£1,821	£5,328	
Total annual cost/patient	£20,642	£25,316	£16,050	
Current market share	8%	49%	44%	
Patient share	27	164	147	
Budget impact	£552,371	£4,149,452	£2,362,251	£7,064,074
Market share assuming positive guidance for eltrombopag	28%	28%	44%	
Patient share	94	94	147	
Budget impact	£1,933,300	£2,371,115	£2,362,251	£6,666,666
Cost difference	-£1,380,929	£1,778,336	£0	**£397,408**

Given the population and market share assumptions outlined above, positive guidance for eltrombopag is estimated to release £996,246 of savings to the NHS annually.

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Costs have been taken from the first year of the economic model. As patients become refractory to more treatments and progress through a cITP treatment pathway they will be at greater risk of receiving expensive rescue medications. The estimates above assume that all patients are at the beginning of a cITP treatment pathway. This may underestimate savings associated with a reduced requirement for rescue treatment in patients receiving TPO-RAs over a longer period of time.

These estimates do not take into account any savings made as a result of a reduced number of bleeding events that require hospitalisation.

References

(1) Bennett D, Hodgson ME, Shukla A, Logie JW. Prevalence of diagnosed adult immune thrombocytopenia in the United Kingdom. *Adv Ther* 2011; 28(12):1096-1104.

(2) European Medicines Agency. CHMP Assessment Report for Revolade. 2010. 10-8-2012.
Ref Type: Online Source

(3) GlaxoSmithKline Group. Revolade Summary of Product Characteristics. 2011.
Ref Type: Report

(4) GlaxoSmithKline. Promacta: Highlights of Prescribing Information. 1-12-2011. 10-8-2012.
Ref Type: Online Source

(5) Scottish Medicines Consortium 2010. Eltrombopag (Revolade). Advice. 2010.
Ref Type: Report

(6) Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. *Br J Haematol* 2003; 120(4):574-596.

(7) Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* 2010; 115(2):168-186.

(8) Stevens W, Koene H, Zwaginga JJ, Vreugdenhil G. Chronic idiopathic thrombocytopenic purpura: present strategy, guidelines and new insights. *Neth J Med* 2006; 64(10):356-363.

(9) Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood* 2009; 113(11):2386-2393.

(10) Neunert C, Lim W, Crowther M, Cohen A, Solberg L, Jr., Crowther MA. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood* 2011; 117(16):4190-4207.

(11) Terrell DR, Beebe LA, Vesely SK, Neas BR, Segal JB, George JN. The incidence of immune thrombocytopenic purpura in children and adults: A critical review of published reports. *Am J Hematol* 2010; 85(3):174-180.

(12) Frederiksen H, Schmidt K. The incidence of idiopathic thrombocytopenic purpura in adults increases with age. *Blood* 1999; 94(3):909-913.

(13) Feudjo-Tepie MA, Robinson NJ, Bennett D. Prevalence of diagnosed chronic immune thrombocytopenic purpura in the US: analysis of a large US claim database: a rebuttal. *J Thromb Haemost* 2008; 6(4):711-712.

(14) Nurden AT, Viallard JF, Nurden P. New-generation drugs that stimulate platelet production in chronic immune thrombocytopenic purpura. *Lancet* 2009; 373(9674):1562-1569.

(15) Stasi R, Evangelista ML, Stipa E, Buccisano F, Venditti A, Amadori S. Idiopathic thrombocytopenic purpura: current concepts in pathophysiology and management. *Thromb Haemost* 2008; 99(1):4-13.

(16) Cines DB, McMillan R. Management of adult idiopathic thrombocytopenic purpura. *Annu Rev Med* 2005; 56:425-442.

(17) Danese MD, Lindquist K, Gleeson M, Deuson R, Mikhael J. Cost and mortality associated with hospitalizations in patients with immune thrombocytopenic purpura. *Am J Hematol* 2009; 84(10):631-635.

(18) Gernsheimer TB, George JN, Aledort LM, Tarantino MD, Sunkara U, Matthew GD et al. Evaluation of bleeding and thrombotic events during long-term use of romiplostim in patients with chronic immune thrombocytopenia (ITP). *J Thromb Haemost* 2010; 8(6):1372-1382.

(19) Handin, Kasper DL, Braunwald E, Fauci AS, et al. Harrison's Principles of Internal Medicine - Bleeding and thrombosis. 16th, 337-343. 2005. New York, NY, McGraw-Hill Medical Publishing Division.
Ref Type: Generic

(20) Mead AJ, Newland AC, Provan D. Adult idiopathic thrombocytopenic purpura. *Hematology* 2003; 8(6):345-357.

(21) Portielje JE, Westendorp RG, Kluin-Nelemans HC, Brand A. Morbidity and mortality in adults with idiopathic thrombocytopenic purpura. *Blood* 2001; 97(9):2549-2554.

(22) Cohen YC, Djulbegovic B, Shamai-Lubovitz O, Mozes B. The bleeding risk and natural history of idiopathic thrombocytopenic purpura in patients with persistent low platelet counts. *Arch Intern Med* 2000; 160(11):1630-1638.

(23) Vianelli N, Valdre L, Fiacchini M, de VA, Gugliotta L, Catani L et al. Long-term follow-up of idiopathic thrombocytopenic purpura in 310 patients. *Haematologica* 2001; 86(5):504-509.

(24) Mathias SD, Gao SK, Miller KL, Cella D, Snyder C, Turner R et al. Impact of chronic Immune Thrombocytopenic Purpura (ITP) on health-related quality of life: a conceptual model starting with the patient perspective. *Health Qual Life Outcomes* 2008; 6:13.

(25) McMillan R, Bussel JB, George JN, Lalla D, Nichol JL. Self-reported health-related quality of life in adults with chronic immune thrombocytopenic purpura. *Am J Hematol* 2008; 83(2):150-154.

(26) Zhou Z, Yang L, Chen Z, Chen X, Guo Y, Wang X et al. Health-related quality of life measured by the Short Form 36 in immune thrombocytopenic purpura: a cross-sectional survey in China. *Eur J Haematol* 2007; 78(6):518-523.

(27) Michel M. Immune thrombocytopenic purpura: epidemiology and implications for patients. *Eur J Haematol Suppl* 2009;(71):3-7.

(28) Horblyuk R, Matzdorff A, Brown TM, et al. Chronic idiopathic thrombocytopenic purpura therapies: the patient's perspective on bothersome effects. EHA European Hematology Association conference . 2009.
Ref Type: Abstract

(29) Grotzinger K, Matzdorff A, Brown TM, et al. Corticosteroids for the treatment of chronic idiopathic thrombocytopenic purpura: patient perceived burden. EHA European Hematology Association conference . 2009.
Ref Type: Abstract

(30) National Institute for Health and Clinical Excellence NICE. Romiplostim FAD. 2010.
Ref Type: Report

(31) National Institute for Health and Clinical Excellence NICE. Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura. Costing template and report. NICE Technology Appraisal Guidance 221. 2011.
Ref Type: Report

(32) National Institute for Health and Clinical Excellence NICE. Eltrombopag for the treatment of chronic immune (idiopathic) thrombocytopenic purpura. Nice Technology Appraisal Guidance 205. 2010.
Ref Type: Report

(33) National Institute for Health and Clinical Excellence NICE. Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura. Nice Technology Appraisal Guidance 221. 2012.
Ref Type: Report

(34) NHS Bedfordshire, NHS Luton. Bedfordshire and Luton Joint Prescribing Commitee (JPC) Report. 2011.
Ref Type: Report

(35) St George's Healtcare - NHS Trust. Treatment pathway for patients with ITP. 2012.
Ref Type: Report

(36) NHS Oxford Radcliffe Hospitals. Guidelines for the investigation and initial treatment of autoimmune thrombocytopenic purpura (AITP) in adults. 2011.
Ref Type: Report

(37) Schlaeppi M, Thornton L. ITP preference study: Physician and Patient results. 11/1216. 2012.
Ref Type: Report

(38) Cheng G, Saleh MN, Marcher C, Vasey S, Mayer B, Aivado M et al. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. *Lancet* 2011; 377:393-402.

(39) GlaxoSmithKline Group. A randomized, double-blind, placebo-controlled phase III study to evaluate the efficacy, safety and tolerability of eltrombopag olamine (SB-497115-GR), a thrombopoietin receptor agonist, administered for 6 months as oral tablets once daily in adult subjects with previously treated chronic idiopathic thrombocytopenic purpura (ITP). RAISE. RAndomized placebo-controlled ITP Study with Eltrombopag. data on file. 2009.
Ref Type: Report

(40) Bussel JB, Cheng G, Saleh MN, Psaila B, Kovaleva L, Meddeb B et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. *N Engl J Med* 2007; 357(22):2237-2247.

(41) GlaxoSmithKline Group. Study TRA100773 Part A: A double-blind, randomized, placebo-controlled, parallel group study to investigate the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of SB-497115-GR, a thrombopoietin receptor agonist, administered at 30, 50 and 75 mg as oral tablets once-daily for 6 weeks to adult male and female subjects with refractory, chronic immune thrombocytopenic purpura. 2007.
Ref Type: Report

(42) Bussel JB, Provan D, Shamsi T, Cheng G, Psaila B, Kovaleva L et al. Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial. *Lancet* 2009; 373(9664):641-648.

(43) GlaxoSmithKline Group. Study TRA100773 Part B: A double-blind, randomized, placebo-controlled, parallel group study to investigate the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of SB-497115-GR, a thrombopoietin receptor agonist, administered at 30, 50 and 75 mg as oral tablets once-daily for 6 weeks to adult male and female subjects with refractory, chronic immune thrombocytopenic purpura. 2007.
Ref Type: Report

(44) Bussel JB, Saleh MN, Grotzinger K, Duh M, Signorovitch J. Improvement in fatigue and health-related quality of life with long-term eltrombopag treatment in adults with chronic

immune thrombocytopenic purpura: the EXTEND study. EHA European Hematology Association conference . 2009.
Ref Type: Abstract

(45) Saleh MN, Cheng G, Bussel JB, Sun H, Mayer B, Bailey C. EXTEND Study Update: Safety and Efficacy of Eltrombopag In Adults with Chronic Immune Thrombocytopenia (ITP) From June 2006 to February 2010. ASH Annual Meeting Abstracts 2010 Nov 19;116(21):67 . 2010.
Ref Type: Abstract

(46) Saleh MN, Cheng G, Bussel J, Burgess P, Marcello L, Bailey C. Safety and Efficacy of EXTENDed Treatment with Eltrombopag in Adults with Chronic Immune Thrombocytopenia (ITP) From June 2006 to February 2011. ASH Annual Meeting Abstracts 2011 Nov 18;118(21):3296. 2011.
Ref Type: Abstract

(47) Psaila B. Efficacy and safety of repeated intermittent treatment with elrombopag in patients with chronic idiopathic idopathic thrombocytopenic purpura (ITP). EHA European Hematology Association conference . 2008.
Ref Type: Abstract

(48) Tomiyama Y, Miyakawa Y, Okamoto S, Katsutani S, Kimura A, koshi Y. Six Month Treatment of Low Dose Eltrombopag Is Efficacious in Japanese Patients with Refractory Chronic Immune Thrombocytopenic Purpura (ITP). ASH Annual Meeting Abstracts 2009 Nov 20;114(22):1324 . 2009.
Ref Type: Abstract

(49) Bussel JB, Psaila B, Saleh MN, et al. Efficacy and safety of repeated intermittent treatment with eltrombopag in patients with chronic idiopathic thrombocytopenic purpura. Blood (ASH Annual Meeting Abstracts): Abs.3431 . 2008.
Ref Type: Abstract

(50) Meyer O, Salama A. Infection-related transient loss of response and other early side effects in chronic ITP during treatment with thrombopoietin mimetics. *Onkologie* 2011; 34(1-2):10-13.

(51) Kuter DJ, Wang F, Dawson K, Grotzinger K, Macahiling C. Patient reported outcomes comparison of chronic immune thrombocytopenia (ITP) patients switched to Promacta and Nplate. ASH Annual Meeting Abstracts . 2011.
Ref Type: Abstract

(52) Haselboeck J, Kaider A, Pabinger I, Panzer S. Platelet Function and Activation in Patients with Immune Thrombocytopenia Treated with Eltrombopag: Comparison with Steroid-Treated and Untreated Patients. ASH Annual Meeting Abstracts 2011 Nov 18;118(21):3280 . 2011.
Ref Type: Abstract

(53) Cooper N, Wong R, Brainsky A, Bailey C. Rate of Cataracts Across the Eltrombopag Clinical Studies in Patients with Chronic Immune Thrombocytopenia. ASH Annual Meeting Abstracts 2011 Nov 18;118(21):1164 . 2011.
Ref Type: Abstract

(54) Olney H, Pabinger I, Mayer B, Bakshi K, Bailey C, Brainsky A. Efficacy and safety of eltrombopag in elderly patients with chronic immune thrombocytopenia: analysis of five clinical trials. ASH Annual Meeting Abstracts . 2011.
Ref Type: Abstract

(55) Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981; 47(1):207-214.

(56) Page LK, Psaila B, Provan D, Michael Hamilton J, Jenkins JM, Elish AS et al. The immune thrombocytopenic purpura (ITP) bleeding score: assessment of bleeding in patients with ITP. *British Journal of Haematology* 2007; 138(2):245-248.

(57) McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993; 31(3):247-263.

(58) Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. *J Pain Symptom Manage* 2002; 24(6):547-561.

(59) Cella D, Beaumont JL, Webster KA, Lai JS, Elting L. Measuring the concerns of cancer patients with low platelet counts: the Functional Assessment of Cancer Therapy--thrombocytopenia (FACT-Th) questionnaire. *Support Care Cancer* 2006; 14(12):1220-1231.

(60) Kuter DJ, Bussel JB, Lyons RM, Pullarkat V, Gernsheimer TB, Senecal FM et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. *Lancet* 2008; 371(9610):395-403.

(61) Bussel JB, Kuter DJ, Pullarkat V, Lyons RM, Guo M, Nichol JL. Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP. *Blood* 2009; 113(10):2161-2171.

(62) Janssens A, Tarantino M, Mazzucconi M, Boccia RV, Lopez-Fernandez MF. Final Results from an International, Multi-Center, Single-Arm Study Evaluating the Safety and Efficacy of Romiplostim in Adults with Primary Immune Thrombocytopenia (ITP). ASH Annual Meeting Abstracts 2011 Nov 18;118(21):3279 . 2011.
Ref Type: Abstract

(63) Bussel JB, Kuter DJ, George JN, McMillan R, Aledort LM, Conklin GT et al. AMG 531, a thrombopoiesis-stimulating protein, for chronic ITP. *N Engl J Med* 2006; 355(16):1672-1681.

(64) Bussel J, Kuter JS, Newland A, de Wolf JT, Wasser J, Chang P. Long-Term Efficacy and Safety of Romiplostim for the Treatment of Patients with Chronic Immune Thrombocytopenia (ITP): 5-Year Update From An Open-Label Extension Study. ASH Annual Meeting Abstracts 2009 Nov 20;114(22):681 . 2009.
Ref Type: Abstract

(65) FDA Advisory Committee Briefing Document. Romiplostim for the treatment of thrombocytopenia in certain adult patients with chronic immune (idiopathic) thrombocytopenia purpura. Biological License Application (BLA) 125268. 12-3-2008.
Ref Type: Report

(66) Kuter DJ, Rummel M, Boccia R, Macik BG, Pabinger I, Selleslag D et al. Romiplostim or standard of care in patients with immune thrombocytopenia. *The New England journal of medicine* 2010; 363:1889-1899.

(67) Shirasugi Y, Ando K, Miyazaki K, Tomiyama Y, Okamoto S, Kurokawa M et al. Romiplostim for the treatment of chronic immune thrombocytopenia in adult Japanese patients: A double-blind, randomized Phase III clinical trial. *International Journal of Hematology* 2011; 94(1):71-80.

(68) Newland A, Caulier MT, Kappers-Klunne M, Schipperus MR, Lefrere F, Zwaginga JJ et al. An open-label, unit dose-finding study of AMG 531, a novel thrombopoiesis-stimulating peptibody, in patients with immune thrombocytopenic purpura. *Br J Haematol* 2006; 135(4):547-553.

(69) Long-term efficacy and safety of Romiplostim treatment of adult patients with chronic immune thrombocytopenia (ITP): Final report from an open-label extension study. 2010.

(70) Shirasugi Y, Ando K, Hashino S, Nagasawa T, Kurata Y, Kishimoto Y et al. A phase II, open-label, sequential-cohort, dose-escalation study of romiplostim in Japanese patients with

chronic immune thrombocytopenic purpura. *International Journal of Hematology* 2009; 90(2):157-165.

(71) Janssens A, Tarantino M, Bird R, Mazzucconi M, Kennedy M, Fernandez M et al. Interim results from an international, multi-center, single-arm study evaluating the safety and efficacy of romiplostim in adults with primary immune thrombocytopenia (ITP). EHA European Hematology Association conference 2011 . 2011.
Ref Type: Abstract

(72) Khellaf M, Michel M, Quittet P, Viallard J-F, Alexis M, Roudot-Thoraval F et al. Romiplostim safety and efficacy for immune thrombocytopenia in clinical practice: 2-Year results of 72 adults in a romiplostim compassionate-use program. *Blood* 2011; 118(16):4338-4345.

(73) National Institute for Health and Clinical Excellence NICE. Eltrombopag for the treatment of chronic idiopathic (immune) thrombocytopenic purpura: Patient Access Scheme Submission. 2011.
Ref Type: Report

(74) National Institute for Health and Clinical Excellence NICE. ERG report - Romiplostim for the treatment of chronic immune or idiopathic thrombocytopenic purpura (ITP) - A single technology appraisal TA221. 2008.
Ref Type: Report

(75) NICE STA maunfacturer's submission by Amgen Inc. Romiplostim for the treatment of chronic immune or Idiopathic Thrombocytopenic Purpura (ITP). 16-10-2008.
Ref Type: Report

(76) European Medicines Agency. NPlate: EPAR Summary for the public. 2010.
Ref Type: Report

(77) Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997; 50(6):683-691.

(78) Bae SH, Ryoo HM, Lee WS., Joo YD, Lee KH, Lee JH et al. High Dose Dexamethasone Vs. Conventional Dose Prednisolone for Adults with Immune Thrombocytopenia: a Prospective Multicenter Phase III Trial. ASH Annual Meeting Abstracts 2010 Nov 19;116(21):3687. 2010.
Ref Type: Abstract

(79) Bellucci S, Charpak Y, Chastang C, Tobelem G. Low doses v conventional doses of corticoids in immune thrombocytopenic purpura (ITP): results of a randomized clinical trial in 160 children, 223 adults. *Blood* 1988; 71(4):1165-1169.

(80) Borte M, Davies SV, Touraine JL, Farber CM, ipsic T, dams C et al. Clinical properties of a novel liquid intravenous immunoglobulin: Studies in patients with immune thrombocytopenic purpura and primary immunodeficiencies. *Transfusion Medicine and Hemotherapy* 2004; 31:126-134.

(81) Bussel JB, Eldor A, Kelton JG, Varon D, Brenner B, Gillis S et al. IGIV-C, a novel intravenous immunoglobulin: evaluation of safety, efficacy, mechanisms of action, and impact on quality of life. *Thromb Haemost* 2004; 91(4):771-778.

(82) Colovic M, Dimitrijevic M, Sonnenburg C, Suvajdzic N, Donfrid M, Bogdanovic A. Clinical efficacy and safety of a novel intravenous immunoglobulin preparation in adult chronic ITP. *Hematol J* 2003; 4(5):358-362.

(83) Ferrari A, Pasqualetti D, Del BP, Gandolfo GM, Chistolini A, Mazzucconi MG. Prednisone versus deflazacort in the treatment of autoimmune thrombocytopenic purpura: evaluation of clinical response and immunological modifications. *Haematologica* 1991; 76(4):342-345.

(84) George JN, Raskob GE, Vesely SK, Moore D, Jr., Lyons RM, Cobos E et al. Initial management of immune thrombocytopenic purpura in adults: a randomized controlled trial comparing intermittent anti-D with routine care. *Am J Hematol* 2003; 74(3):161-169.

(85) Godeau B, Lesage S, Divine M, Wirquin V, Farcet JP, Bierling P. Treatment of adult chronic autoimmune thrombocytopenic purpura with repeated high-dose intravenous immunoglobulin. *Blood* 1993; 82(5):1415-1421.

(86) Godeau B, Caulier MT, Decuypere L, Rose C, Schaeffer A, Bierling P. Intravenous immunoglobulin for adults with autoimmune thrombocytopenic purpura: results of a randomized trial comparing 0.5 and 1 g/kg b.w. *Br J Haematol* 1999; 107(4):716-719.

(87) Godeau B, Chevret S, Varet B, Lefrere F, Zini JM, Bassompierre F et al. Intravenous immunoglobulin or high-dose methylprednisolone, with or without oral prednisone, for adults with untreated severe autoimmune thrombocytopenic purpura: a randomised, multicentre trial. *Lancet* 2002; 359(9300):23-29.

(88) Jacobs P, Wood L, Novitzky N. Intravenous gammaglobulin has no advantages over oral corticosteroids as primary therapy for adults with immune thrombocytopenia: a prospective randomized clinical trial. *Am J Med* 1994; 97(1):55-59.

(89) Mazzucconi MG, Francesconi M, Fidani P, Di NG, Gandolfo GM, Afeltra A et al. Treatment of idiopathic thrombocytopenic purpura (ITP): results of a multicentric protocol. *Haematologica* 1985; 70(4):329-336.

(90) Newman GC, Novoa MV, Fodero EM, Lesser ML, Woloski BM, Bussel JB. A dose of 75 microg/kg/d of i.v. anti-D increases the platelet count more rapidly and for a longer period of time than 50 microg/kg/d in adults with immune thrombocytopenic purpura. *Br J Haematol* 2001; 112(4):1076-1078.

(91) Praituan W, Rojnuckarin P. Faster platelet recovery by high-dose dexamethasone compared with standard-dose prednisolone in adult immune thrombocytopenia: A prospective randomized trial. *Journal of Thrombosis and Haemostasis* 2009; 7(6):1036-1038.

(92) Shen ZX, Li JM, Wang ZY, Han ZC, Caen JP, Bellucci SA. Thrombocytopoietic effect of heparin given in chronic immune thrombocytopenic purpura. *Lancet* 1995; 346(8969):220-221.

(93) Arnold DM, et al. Rituximab added to standard therapy for non-splenectomized patients with immune thrombocytopenia: a randomised, double-blind, placebo-controlled trial. EHA European Hematology Association conference 2011 . 2011.
Ref Type: Abstract

(94) Gudbrandsdottir S, Frederiksen H, Helleberg I, Jensen B, Kjeldsen L, Klausen T et al. Efficacy of rituximab in combination with dexamethasone vs dexamethasone in newly diagnosed patients with primary immune thrombocytopenia - An interim analysis of a prospective randomised study. *Haematologica Conference: 15th Congress of the European Hematology Association, EHA 2010 Barcelona Spain Conference Start: 20100610 Conference End: 20100613 Conference Publication: (var pagings) 95 (pp 253), 2010 Date of Publication: June 2010* 2010;(var.pagings):June.

(95) Li Z, Mou W, Lu G, Cao J, He X, Pan X et al. Low-dose rituximab combined with short-term glucocorticoids up-regulates Treg cell levels in patients with immune thrombocytopenia. *International journal of hematology* 2011; 93:91-98.

(96) A prospective randomized study comparing rituximab and dexamethasone vs dexamethasone alone in ITP: Results of final analysis and long term follow up. 2008.

(97) Hasan A, Michel M, Patel V, Stasi R, Cunningham RS, Leonard JP et al. Repeated courses of rituximab in chronic ITP: Three different regimens. *American journal of hematology* 2009; 84:661-665.

(98) Alasfoor K, Alrasheed M, Alsayegh F, Mousa SA. Rituximab in the treatment of idiopathic thrombocytopenic purpura (ITP). *Ann Hematol* 2009; 88(3):239-243.

(99) Aledort LM, Salama A, Kovaleva L, Robak T, Newland AC, Nugent DJ et al. Efficacy and safety of intravenous anti-D immunoglobulin (Rhophylac) in chronic immune thrombocytopenic purpura. *Hematology* 2007; 12(4):289-295.

(100) Colovic M, Suvajdzic N, Colovic N, Tomin D, Vidovic A, Palibrk V. Mycophenolate mophetil therapy for chronic immune thrombocytopenic purpura resistant to steroids, immunosuppressants, and/or splenectomy in adults. *Platelets* 2011; 22(2):153-156.

(101) Cooper N, Stasi R, Cunningham-Rundles S, Feuerstein MA, Leonard JP, Amadori S et al. The efficacy and safety of B-cell depletion with anti-CD20 monoclonal antibody in adults with chronic immune thrombocytopenic purpura. *Br J Haematol* 2004; 125(2):232-239.

(102) Garcia-Chavez J, Majluf-Cruz A, Montiel-Cervantes L, Esparza MG, Vela-Ojeda J. Rituximab therapy for chronic and refractory immune thrombocytopenic purpura: a long-term follow-up analysis. *Ann Hematol* 2007; 86(12):871-877.

(103) Godeau B, Oksenhendler E, Bierling P. Dapsone for autoimmune thrombocytopenic purpura. *Am J Hematol* 1993; 44(1):70-72.

(104) Godeau B, Porcher R, Fain O, Lefrere F, Fenaux P, Cheze S et al. Rituximab efficacy and safety in adult splenectomy candidates with chronic immune thrombocytopenic purpura: results of a prospective multicenter phase 2 study. *Blood* 2008; 112(4):999-1004.

(105) Gomez-Almaguer D, Solano-Genesta M, Tarin-Arzaga L, Herrera-Garza JL, Cantu-Rodriguez OG, Gutierrez-Aguirre CH et al. Low-dose rituximab and alemtuzumab combination therapy for patients with steroid-refractory autoimmune cytopenias. *Blood* 2010; 116(23):4783-4785.

(106) Gringeri A, Cattaneo M, Santagostino E, Mannucci PM. Intramuscular anti-D immunoglobulins for home treatment of chronic immune thrombocytopenic purpura. *Br J Haematol* 1992; 80(3):337-340.

(107) Hernandez F, Linares M, Colomina P, Pastor E, Cervero A, Perez A et al. Dapsone for refractory chronic idiopathic thrombocytopenic purpura. *Br J Haematol* 1995; 90(2):473-475.

(108) Hou M, Peng J, Shi Y, Zhang C, Qin P, Zhao C et al. Mycophenolate mofetil (MMF) for the treatment of steroid-resistant idiopathic thrombocytopenic purpura. *Eur J Haematol* 2003; 70(6):353-357.

(109) Julia A, Kovaleva L, Loria S, Alberca I, Hernandez F, Sandoval V et al. Clinical efficacy and safety of Flebogammadif, a new high-purity human intravenous immunoglobulin, in adult patients with chronic idiopathic thrombocytopenic purpura. *Transfusion Medicine* 2009; 19(5):260-268.

(110) Kim YL J. The feasibility of high-dose dexamethasone (HD-DEX) in idiopathic thrombocytopenic purpura (ITP) in adults; a multicenter study in Korea. Blood (ASH Annual Meeting Abstracts) 4009(106). 2005.
Ref Type: Abstract

(111) Kueh YK. Vincristine therapy in refractory chronic idiopathic thrombocytopenic purpura. *Ann Acad Med Singapore* 1982; 11(2):290-293.

(112) Medeot M, Zaja F, Vianelli N, Battista M, Baccarani M, Patriarca F et al. Rituximab therapy in adult patients with relapsed or refractory immune thrombocytopenic purpura: long-term follow-up results. *Eur J Haematol* 2008; 81(3):165-169.

(113) Montes-Gaisan C, Nunez J, Yanez L, Bermudez A, Ruiz M, Olaya I et al. Rituximab in the treatment of patients with refractory idiopathic thrombocytopenic purpura. *Haematologica Conference: 14th Congress of the European Hematology Association Berlin Germany Conference Start: 20090604 Conference End: 20090607 Conference Publication: (var pagings) 94 (pp 95-96), 2009 Date of Publication: June 2009* 2009;(var.pagings):June.

(114) Nalli G, Sajeva MR, Maffe GC, Ascari E. Danazol therapy for idiopathic thrombocytopenic purpura (ITP). *Haematologica* 1988; 73(1):55-57.

(115) Pasa S, Altintas A, Cil T, Danis R, Ayyildiz O. The efficacy of rituximab in patients with splenectomized refractory chronic idiopathic thrombocythopenic purpura. *J Thromb Thrombolysis* 2009; 27(3):329-333.

(116) Penalver FJ, Jimenez-Yuste V, Almagro M, Alvarez-Larran A, Rodriguez L, Casado M et al. Rituximab in the management of chronic immune thrombocytopenic purpura: an effective and safe therapeutic alternative in refractory patients. *Ann Hematol* 2006; 85(6):400-406.

(117) Provan D, Moss AJ, Newland AC, Bussel JB. Efficacy of mycophenolate mofetil as single-agent therapy for refractory immune thrombocytopenic purpura. *Am J Hematol* 2006; 81(1):19-25.

(118) Reiner A, Gernsheimer T, Slichter SJ. Pulse cyclophosphamide therapy for refractory autoimmune thrombocytopenic purpura. *Blood* 1995; 85(2):351-358.

(119) Robak T, Salama A, Kovaleva L, Vyhovska Y, Davies SV, Mazzucconi MG et al. Efficacy and safety of Privigen, a novel liquid intravenous immunoglobulin formulation, in adolescent and adult patients with chronic immune thrombocytopenic purpura. *Hematology* 2009; 14(4):227-236.

(120) Robak T, Mainau C, Pyringer B, Chojnowski K, Warzocha K, Dmoszynska A et al. Efficacy and safety of a new intravenous immunoglobulin 10% formulation (octagam 10%) in patients with immune thrombocytopenia. *Hematology* 2010; 15(5):351-359.

(121) Santaro CB F, de Angelis G. Rituximab in refractory idiopathic thrombocytopenic purpura (ITP). ASH Annual Meeting Abstracts 108(3979). 2006.
Ref Type: Abstract

(122) Scaradavou A, Woo B, Woloski BM, Cunningham-Rundles S, Ettinger LJ, Aledort LM et al. Intravenous anti-D treatment of immune thrombocytopenic purpura: experience in 272 patients. *Blood* 1997; 89(8):2689-2700.

(123) Stasi R, Brunetti M, Pagano A, Stipa E, Masi M, Amadori S. Pulsed intravenous high-dose dexamethasone in adults with chronic idiopathic thrombocytopenic purpura. *Blood Cells Mol Dis* 2000; 26(6):582-586.

(124) Stasi R, Pagano A, Stipa E, Amadori S. Rituximab chimeric anti-CD20 monoclonal antibody treatment for adults with chronic idiopathic thrombocytopenic purpura. *Blood* 2001; 98(4):952-957.

(125) Varga G, Volkova Z, Leibl H, Gasztonyi Z, Hlusi A, Mayer J. Efficacy and safety of the new intravenous immunoglobulin IGIV 10% in adults with chronic idiopathic thrombocytopenic purpura. Transfusion Medicine and Hemotherapy; 33(6):509-14. 2006.
Ref Type: Abstract

(126) Yassin M, El-Ayyoubi H, Muhammed H, Kamzoul R, Al-Badri M, Al-Sabbah H. Efficacy and Safety of Six Doses of Rituximab (375mg/m2) in Treatment of Chronic Refractory Immune

Thrombocytopenia an Experience from QATAR. Haematologica.Conference: 16th Congress of the European Hematology Association, EHA 2011 London United Kingdom.Conference Start: 20110609 Conference End: 20120612.Conference Publication: 96s2 (pp 648), 2011.Date of publication . 2011.
Ref Type: Abstract

(127) Zaja F, Vianelli N, Sperotto A, De VS, Iacona I, Zaccaria A et al. B-cell compartment as the selective target for the treatment of immune thrombocytopenias. *Haematologica* 2003; 88(5):538-546.

(128) Gutierrez-Espindola GR, Morales-Polanco MR, Guerrero-Rivera S, Talavera JO, Sanchez-Valle E, Gomez-Morales E et al. High doses of dexamethasone in adult patients with idiopathic thrombocytopenic purpura. *Arch Med Res* 2003; 34(1):31-34.

(129) Bussel J, 2012, Brainsky A. Cumulative Response to Eltrombopag and Impact of the Number of Prior ITP Therapies: Interim Results of a Long-Term Extension Study. ASH Annual Meeting Abstracts 2011 Nov 18;118(21):3297. 2011.
Ref Type: Abstract

(130) Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions v 5.1.0. 2011.
Ref Type: Report

(131) FDA Advisory Committee Briefing Document. Promacta (Eltrombopag) tablets: Application number 022291. Application number 022291. 20-11-2008.
Ref Type: Report

(132) Mowatt G, Boachie C, Crowther M, Fraswer C, Hernandez R, Jia X et al. Romiplostim for the treatment of chronic immune or idiopathic thrombocytopenic purpura: a single technology appraisal. *Health Technology Assessment* 2009; 13(Suppl 2):63-68.

(133) Boyers D, Jia X, Jenkinson D, Mowatt G. Eltrombopag for the treatment of chronic immune or idiopathic thrombocytopenic purpura: a NICE single technology appraisal. *Pharmacoeconomics* 2012; 30(6):483-495.

(134) NICE STA maunfacturer's submission by GSK. Eltrombopag (Revolade®) for the treatment of chronic immune (idiopathic) thrombocytopenic purpura. 9-10-2009.
Ref Type: Report

(135) Szende A, Brazier J, Schaefer C, Deuson R, Isitt JJ, Vyas P. Measurement of utility values in the UK for health states related to immune thrombocytopenic purpura. *Curr Med Res Opin* 2010; 26(8):1893-1903.

(136) British National Formulary. http://www bnf org/bnf/ [2008 [cited 2008 Oct. 13];

(137) Snyder CF, Mathias SD, Cella D, Isitt JJ, Wu AW, Young J. Health-related quality of life of immune thrombocytopenic purpura patients: results from a web-based survey. *Curr Med Res Opin* 2008; 24(10):2767-2776.

(138) George JN, Mathias SD, Go RS, Guo M, Henry DH, Lyons RM et al. Improved quality of life for romiplostim-treated patients with chronic immune thrombocytopenic purpura: results from two randomized, placebo-controlled trials. *Br J Haematol* 2009; 144(3):409.

(139) Sanz MA, Aledort L, Mathias SD, Wang X, Isitt JJ. Analysis of EQ-5D scores from two phase 3 clinical trials of romiplostim in the treatment of immune thrombocytopenia (ITP). *Value Health* 2011; 14(1):90-96.

(140) Brazier J, Green C, Kanis J. A systematic review of health state utility values for osteoporosis-related conditions. *Osteoporosis Int* 2002; 13(10):768-776.

(141) Iskedjian M, Tinmouth AT, Arnold DM, Deuson R, Isitt JJ, Mikhael J. Elicitation of utility scores in Canada for immune thrombocytopenia treated with romiplostim or watch and rescue. *J Med Econ* 2012; 15(2):313-331.

(142) Leontiadis GI, Sreedharan A, Dorward S. Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding. *Health Technology Assessment* 2007; 11(51).

(143) Patient access scheme submission template prepared by Amgen Inc. Romiplostim for the treatment of chronic idiopathic (immune) thrombocytopenic purpura. 2009.
Ref Type: Report

(144) Kuter DJ, Bussel JB, Lyons RM, Pullarkat V, Gernsheimer TB, Senecal FM et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. *The Lancet* 2008; 371(9610):20080202-08-20080202403.